UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

PACIRA PHARMACEUTICALS, INC., DR. LOREN J. HARRIS, and DR. JOSEPH W. BELL, Plaintiffs, v. UNITED STATES FOOD & DRUG ADMINISTRATION; UNITED STATES OF AMERICA; DR. STEPHEN OSTROFF, in his official capacity as Acting Commissioner of Food and Drugs; UNITED STATES DEPARTMENT OF HEALTH & HUMAN SERVICES; and SYLVIA MATHEWS BURWELL, in her official capacity as Secretary of the Department of Health & Human Services, Defendants.	Civil Action No. _____________

COMPLAINT FOR
DECLARATORY AND INJUNCTIVE RELIEF

INTRODUCTION

1. Through this Complaint against the United States and, in particular, the Food and Drug Administration ("FDA"), Pacira Pharmaceuticals, Inc. ("Pacira") seeks to establish its right to speak in a truthful and non-misleading fashion about lawful uses of its product EXPAREL.

2. Pacira is a young pharmaceutical company focused on the development of non-opioid pain medications. It markets one key product, EXPAREL, an innovative local anesthetic for controlling postsurgical pain through administration into the surgical site. Pacira and its predecessor companies worked for many years to develop EXPAREL, which combines bupivacaine (a local anesthetic that has been widely used in the United States since approved by FDA in 1972) with a novel delivery platform called DepoFoam that allows the drug to be administered with precision and provide more extended pain relief than plain bupivacaine.

3. Pacira demonstrated EXPAREL's safety and effectiveness in providing postsurgical pain control through two clinical trials. Pacira conducted these pivotal studies in two very different surgical procedures: bunionectomies, which involve an orthopedic and hard tissue site, and hemorrhoidectomies, a highly vascular soft tissue site. These two successful trials in markedly different surgical sites provide a valid basis—consistent with FDA's own practice—from which to determine that EXPAREL can be used safely and effectively in any surgical site.

4. Pacira submitted a New Drug Application ("NDA") to FDA seeking EXPAREL's approval for use in surgical sites, based on these pivotal trials. Consistent with scientific, medical, and regulatory practice, FDA granted Pacira a broad approval for EXPAREL on October 28, 2011. Under FDA regulations, the "Indications and Usage" section of the FDA-approved label describes the drug's approved uses. And according to the "Indications and

Usage" section of the FDA-approved label, "EXPAREL is a liposome injection of bupivacaine, an amide-type local anesthetic, indicated for administration into the surgical site to produce postsurgical analgesia."

5. When the drug launched commercially in 2012, physicians were quick to embrace use of EXPAREL for their patients because it provided safe and effective postsurgical pain control. In addition, EXPAREL is not an opioid, and as the prescription opioid addiction problem reached epidemic proportions in the United States, many physicians desired opioid alternatives to provide postsurgical pain relief.

6. Consistent with FDA's approval of EXPAREL, Pacira spoke with physicians, surgeons, and anesthesiologists about use of EXPAREL to produce postsurgical analgesia in different surgical sites. Pacira communicated with physicians about EXPAREL in truthful and non-misleading ways, explaining to them that the drug had been approved by FDA "for administration into the surgical site to produce postsurgical analgesia," and sharing with physicians the actual experiences that other physicians had administering EXPAREL in different surgical sites. During this time, Pacira submitted promotional materials to FDA, as FDA requires.

7. In September 2014, nearly three years after FDA approved EXPAREL for use in surgical sites generally and after receiving, without objection, three years worth of promotional materials from Pacira promoting EXPAREL for that broad indication, FDA issued Pacira a formal Warning Letter demanding that "Pacira immediately cease" sharing with surgeons, anesthesiologists, and other sophisticated audiences certain information about using EXPAREL outside of a bunionectomy or hemorrhoidectomy.

8. The Warning Letter asserted that some of Pacira's speech was criminal because it established "new intended uses" for EXPAREL and that other speech was criminal because it lacked the support of two clinical trials—the exceedingly high level of evidentiary support that the Food, Drug and Cosmetic Act ("FDCA") requires for *new drug approval* and which FDA, by regulation, requires a manufacturer to have before making any efficacy or comparative claims. FDA's attempt to silence Pacira's truthful and non-misleading speech is inconsistent with the FDCA and the First Amendment of the Constitution.

9. EXPAREL's label reflects that it is approved for use in surgical sites generally. Nonetheless, FDA's Warning Letter stated that speech by Pacira about use of EXPAREL in specific surgical sites other than bunionectomy and hemorrhoidectomy constitutes a criminal violation of the FDCA. Neither the FDCA nor the First Amendment permits FDA to restrict Pacira's speech about specific uses within the broad indication for which EXPAREL was approved.

10. FDA's Warning Letter suggests that FDA is attempting retroactively to revise EXPAREL's label to limit the product's approved indication to use in connection with bunionectomy or hemorrhoidectomy. The FDCA does not permit FDA to make such labeling changes except in limited circumstances where FDA becomes aware of new safety information about a serious risk associated with use of the drug after approval of the drug, and only after following designated procedures. *See* 21 U.S.C. §§ 355(o)(4), 355-1. FDA has taken none of the steps necessary to revise EXPAREL's label, nor could it, in light of EXPAREL's exceptional safety record.

11. Even if EXPAREL's approved uses (its so-called "on-label" uses) were limited to bunionectomy and hemorrhoidectomy (and they are not), the FDCA would not (and could not,

under the First Amendment) authorize FDA to forbid Pacira's truthful and non-misleading speech to surgeons and anesthesiologists about their lawful use of EXPAREL to control post-operative pain in other surgical sites (*i.e.*, supposed "off-label" uses). Pacira's pivotal studies demonstrating the safety and efficacy of EXPAREL in bunionectomies and hemorrhoidectomies provide a valid basis—consistent with FDA's own guidance—from which to extrapolate that EXPAREL can be used safely and effectively in other surgical sites. FDA could not prohibit such speech as violating the FDCA, as FDA asserted in the Warning Letter. As the Second Circuit has made clear, "the government cannot prosecute pharmaceutical manufacturers and their representatives under the FDCA for speech promoting the lawful, off-label use of an FDA-approved drug." *United States v. Caronia*, 703 F.3d 149, 169 (2d Cir. 2012).

12. Basic principles of Due Process reinforce the limitations on FDA's authority. Especially where the government attempts to silence speech, its rules must be clear and provide fair notice. Where, as with EXPAREL, FDA has approved the drug for "administration into the surgical site to produce postsurgical analgesia," without limiting the indication to any specific "surgical site," the government cannot maintain that it is criminal to promote use of the approved drug in different "surgical site[s]."

13. In the Warning Letter, FDA also sought to preclude Pacira from making certain truthful and non-misleading statements about uses of EXPAREL that are indisputably on-label. Under FDA regulations, any statements about the effectiveness of EXPAREL, or that compare it to other products, are prohibited unless those statements are supported by what FDA deems "substantial evidence." FDA regulations require two adequate and well-controlled studies (*i.e.*, randomized, controlled, blinded studies with pre-specified endpoints) to satisfy the "substantial evidence" standard and for comparative claims, FDA requires two such trials that compare the

products head-to-head.[1] In the absence of evidence meeting this high bar, FDA deems any such speech by the company inherently false or misleading and, on that basis, a crime. 21 C.F.R. § 202.1(e)(6)(i)-(ii); *see* 21 U.S.C. §§ 352(a), 331(a).

14. The regulations requiring adequate and well-controlled investigations to support comparative claims apply only to pharmaceutical manufacturers; there are no comparable regulations applicable to medical device manufacturers, or to any other speaker. Notably, FDA's prohibitions on Pacira's speech about effectiveness or comparison to other products apply even when the subject speech concerns the precise purpose for which FDA approved EXPAREL. For example, even though FDA's own medical reviewer acknowledged that a pivotal study of EXPAREL "demonstrated a statistically significant reduction in pain through 72 hours compared to placebo (p<0.0001)," Arthur Simone, Amended Clinical Review of EXPAREL 89 (Oct. 7, 2011) ("FDA Medical Review"), FDA's Warning Letter declared that claims "suggesting that Exparel has demonstrated pain control beyond 24 hours are misleading," and therefore a criminal violation. FDA did not suggest this information could be shared if accompanied by further disclaimers, but instead invoked a categorical ban against such statements. The FDCA does not grant FDA such authority over pharmaceutical manufacturers' speech. And if it did, the statute would violate the First Amendment.

15. In response to the Warning Letter, Pacira submitted a letter on October 6, 2014, disputing FDA's assertion that promotion of EXPAREL for use in laparoscopic cholecystectomy

[1] *See, e.g.*, 21 C.F.R. § 314.126(a) (stating that "[r]eports of adequate and well-controlled investigations provide the primary basis for determining whether there is 'substantial evidence' to support the claims of effectiveness for new drugs" and describing the features of "adequate and well-controlled investigations"); *id.* § 316.3(b)(3) (stating that "direct comparative clinical trials" are generally necessary "to support a comparative effectiveness claim for two different drugs"); Letter from FDA, Division of Drug Marketing, Advertising, and Communications ("DDMAC"), to G. Pohl-Boskamp, Arbor Pharmaceuticals, Inc. at 3-4 (Apr. 26, 2011) (stating that "[g]enerally, claims of superiority must be supported by two adequate and well-controlled head-to-head clinical trials comparing appropriate doses and dose regimes of a drug and a comparator drug").

and open colectomy and other surgeries was beyond the FDA-approved indication. Pacira further contested the Warning Letter's assertion that Pacira's claim that EXPAREL controls pain for up to 72 hours lacks support. FDA refused to discuss the substance of these issues with Pacira, however, and when the Agency persisted in demanding that Pacira "correct" its speech, Pacira acquiesced. At FDA's direction, Pacira issued a statement that "corrected" Pacira's prior statements by emphasizing points from an FDA analysis of EXPAREL data that FDA believed undermined Pacira's speech. Pacira also agreed to refrain from disseminating certain promotional materials that it had previously been distributing relating to administration of EXPAREL in surgical sites other than bunionectomy and hemorrhoidectomy.

16. Pacira made clear to FDA, however, that it was not acquiescing in FDA's positions as to the truthfulness of Pacira's statements, or its right to speak. Pacira explained its disagreement with FDA's position in its October 6, 2014 response to the Warning Letter and followed up with the Agency in a November 19, 2014 letter. On June 23, 2015, Pacira sent FDA a further white paper explaining in greater detail why FDA's positions were inconsistent with the scientific evidence and FDA's own regulations. In the June Letter, Pacira (again) asked for a meeting with FDA to discuss these issues. Despite Pacira's requests that FDA explain why speech consistent with EXPAREL's general "Indications and Usage" section could be criminal, FDA refused and continues to refuse to meet with Pacira or otherwise explain its position.

17. On July 24, 2015, without ever responding to Pacira's arguments about why its speech is permissible under the FDCA and FDA regulations, FDA sent Pacira a letter stating that it regarded the Warning Letter "closed." The "close-out" letter noted FDA's assertion that Pacira's speech was "violative" of the FDCA, recited that Pacira had "[c]eased dissemination of all materials such as those containing statements referenced in the Warning Letter," and

"reminded [Pacira] of [its] continuing obligation to ensure that all [its] promotional materials comply with each applicable requirement of the [FDCA] and FDA implementing regulations." The close-out letter altogether ignores Pacira's arguments and even attempts to erase certain of Pacira's communications from the record.

18. FDA's speech restrictions have harmed and continue to harm Pacira, the plaintiff doctors, other health care providers, and their patients. These restrictions on Pacira's truthful and non-misleading speech about EXPAREL have harmed the Company's commercial interests. They have inhibited the Company's ability to advance its public health mission by providing information to physicians about alternatives to opioids for surgical pain relief. And the plaintiff doctors and other physicians, as well as their patients, have been harmed because the restrictions FDA imposes on Pacira impair its ability to share important information about EXPAREL.

19. Pacira and the plaintiff doctors bring this suit to obtain declaratory and injunctive relief under the Constitution and laws of the United States so that Pacira may, once again, speak in truthful and non-misleading ways about EXPAREL—without fear of having enforcement actions taken against it.

PARTIES

20. Plaintiff Pacira Pharmaceuticals, Inc. is a Delaware corporation with its principal place of business located at 5 Sylvan Way, Suite 300, Parsippany, New Jersey 07054.

21. Plaintiff Dr. Loren J. Harris, a resident of New York County, New York, is a physician who currently serves as the Chief of General Thoracic Surgery at Maimonides Medical Center in Brooklyn, New York. Dr. Harris regularly administers EXPAREL to his patients to provide postsurgical pain relief and is interested in receiving truthful, non-misleading

information from Pacira about use of the drug in other surgical sites, such as the abdomen and the chest, and about other surgeons' experiences with EXPAREL.

22. Plaintiff Dr. Joseph W. Bell is a physician in private practice specializing in general surgery. He is affiliated with Saratoga Center for General and Minimally Invasive Surgery in Saratoga Springs, New York. Dr. Bell regularly administers EXPAREL to his patients to provide postsurgical pain relief and is interested in receiving truthful, non-misleading information from Pacira about how other surgeons have used the drug. Dr. Bell is a resident of Montgomery County, New York.

23. Defendant U.S. Food and Drug Administration is a federal agency within the U.S. Department of Health & Human Services ("HHS"). Under the Federal Food, Drug, and Cosmetic Act, FDA is responsible for approving and otherwise regulating drugs, medical devices, and other products. FDA's headquarters are located in Silver Spring, Maryland.

24. Defendant U.S. Department of Health & Human Services is an executive department in the United States. HHS oversees FDA, including its execution and administration of the FDCA. HHS's headquarters are located in Washington, D.C.

25. Defendant Dr. Stephen Ostroff is sued in his official capacity as the Acting Commissioner of Food and Drugs, the most senior official at FDA. As Acting Commissioner, Dr. Ostroff is directly responsible for the execution and administration of the FDCA and the regulations promulgated thereunder.

26. Defendant Sylvia Mathews Burwell is sued in her official capacity as the Secretary of HHS. Secretary Burwell is Acting Commissioner Ostroff's immediate supervisor as well as the immediate supervisor of the HHS Office of the Inspector General ("HHS OIG") and,

as such, Secretary Burwell is responsible for the execution and administration of the FDCA and the regulations promulgated thereunder.

27. The United States of America, through its agencies and instrumentalities, including FDA, HHS OIG and Department of Justice, is responsible for enforcement of the FDCA.

JURISDICTION AND VENUE

28. This action seeks declaratory relief under the Federal Declaratory Judgment Act, 28 U.S.C. § 2201.

29. This Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. § 1331 because all causes of action arise under the Constitution and the laws of the United States. Pacira's claims against the defendants arise under the First and Fifth Amendments. Pacira also asserts claims that arise under the Administrative Procedure Act, 5 U.S.C. § 702, as Pacira seeks judicial review of certain FDA regulations and actions that are "contrary to constitutional right," "in excess of statutory jurisdiction, authority, or limitations," and "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2).

30. Venue is proper in this judicial district pursuant to 28 U.S.C. § 1391(e)(1)(C).

31. An actual, justiciable controversy currently exists between the parties concerning whether the FDCA does, or FDA may, restrict and ban Pacira's truthful and non-misleading speech about lawful uses of its product, including by retroactively adopting a narrow interpretation of EXPAREL's label.

32. Declaratory relief will resolve this controversy and eliminate the chill that FDA's regulations and Warning Letter currently exert on Pacira's First Amendment-protected speech.

33. A preliminary injunction preventing FDA from taking enforcement action against Pacira for truthful and non-misleading speech about lawful uses of EXPAREL or from categorically deeming speech "misleading," and therefore criminal when not supported by two well-controlled, randomized, and blinded clinical studies will protect Pacira's First Amendment rights from ongoing harm while this litigation is pending.

34. A permanent injunction preventing FDA from taking enforcement action against Pacira for truthful and non-misleading speech about lawful uses of EXPAREL or from categorically deeming speech "misleading" and therefore criminal when not supported by two well-controlled, randomized, and blinded clinical studies will protect Pacira's First Amendment rights prospectively after the final resolution of this matter.

LEGAL AND REGULATORY FRAMEWORK

The New Drug and Drug Label Approval Process

35. No new drug may be introduced into interstate commerce without following the rigorous NDA process established by the Federal Food, Drug, and Cosmetic Act ("FDCA"). *See* 21 U.S.C. § 355. An NDA applicant is required to file a number of items with its application, including *inter alia*, full reports of investigations demonstrating that the drug is safe and effective, information about the drug's composition, proposed labeling for the drug, and a description of the methods and facilities used for the manufacture, processing and packaging of the drug. *Id.* § 355(b)(1)(A)-(G).

36. As part of the NDA approval process, FDA approves specific prescribing information in the form of a package insert, or "PI." 21 C.F.R. §§ 201.56, 201.57. Generally, FDA requires that all drug labels, or PIs, contain a summary of the essential scientific information needed for the safe and effective use of the drug, be neither false nor misleading, and

be based whenever possible on data derived from human experience. *Id*. § 201.56(a)(1)-(3). The PI for prescription drugs must include sections covering, *inter alia*, Indications and Usage, Dosage and Administration, Dosage Forms and Strengths, Contraindications, Warnings, Precautions, Adverse Reactions, Drug Interactions, and Use in Specific Populations. *Id*. § 201.56(d)(1). FDA must approve all information in the PI before a drug is approved to be marketed. FDA approves the PI only after a thorough review and iterative negotiation with the drug manufacturer.

37. Each of these sections of the PI is required to conform to specific regulatory requirements. For example, the Indications and Usage section must contain "[a] concise statement of each of the product's indications, as required under paragraph (c)(2) of this section, with any appropriate subheadings," stating "that the drug is indicated for the treatment, prevention, mitigation, cure or diagnosis of a recognized disease or condition, or of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition." 21 C.F.R. § 201.57(a)(6), (c)(2). The approved indications for a drug, as described in the Indications and Usage section of the PI, are—according to FDA—"those for which FDA has found [the drug] to be safe and effective." *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, Final Rule, 71 Fed. Reg. 3,922, 3,944 (Jan. 24, 2006).

38. The Dosage and Administration section must state the recommended dosage, including the dosage range, dosages for different indications and subpopulations, the intervals recommended for dose, and other dosage considerations. 21 C.F.R. § 201.57(c)(3).

39. The Clinical Studies section "must discuss those clinical studies that facilitate an understanding of how to use the drug safely and effectively." 21 C.F.R. § 201.57(c)(15). FDA

has stressed that "the 'Clinical Studies' section," rather than Indications and Usage section, "is the appropriate section of labeling to discuss the details (*e.g.*, trial design, outcome) of clinical trials."[2] The Indications and Usage section, by contrast, is the correct section of the label to discuss approved indications and limitations. If a drug has been approved for a general indication based on clinical trials in limited clinical settings, the Clinical Studies section may contain information for physicians to this effect even while the drug remains approved for the general indication.

Drugs May Lawfully Be Prescribed Beyond FDA-Approved Indications

40. Once FDA approves a drug as safe and effective and approves the drug's PI, that drug may lawfully be prescribed and used for *any* purpose, even those not consistent with or included within the drug's approved indications as reflected in the label. "[O]nce a [drug] product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens of patient populations that are not included in approved labeling." *Citizen Petition Regarding the Food and Drug Administration's Policy on Promotion of Unapproved Uses of Approved Drugs and Devices; Request for Comments*, 59 Fed. Reg. 59,820, 59,821-22 (Nov. 18, 1994) (citation omitted) (alteration in original). The use of a drug for purposes other than its approved indications is often referred to as "off-label" drug use.

41. "[O]ff-label drug usage is not unlawful." *Caronia*, 703 F.3d at 166. "[P]hysicians can prescribe, and patients can use, drugs for off-label purposes." *Id.*; *see also* 21 U.S.C. § 396 (providing that the FDCA does not "limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease").

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[2] 71 Fed. Reg. at 3,944.

42. Indeed, "FDA has long recognized that in certain circumstances, new (off-label) uses of approved products are appropriate, rational, and accepted medical practice." *Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices*, 63 Fed. Reg. 31,143, 31,153 (June 8, 1998) (codified at 21 C.F.R. pts. 16, 99). According to FDA, "off-label uses or treatment regimens may be important therapeutic options and may even constitute a medically recognized standard of care." FDA, *Draft Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices* 2 (Dec. 2011); *see also* American Academy of Pediatrics, Committee on Drugs, *Uses of Drugs Not Described in the Package Insert (Off-Label Uses)*, 110 Pediatrics 181, 182 (2002) (explaining that in some cases, "the practice of medicine may require a practitioner to use drugs off-label to provide the most appropriate treatment for a patient").

43. In practice, "[o]ff-label use is widespread in the medical community and often is essential to giving patients optimal medical care." James Beck & Elizabeth D. Azari, FDA, *Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 Food & Drug L.J. 71, 72 (1998), *quoted in Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 351 n.5 (2001).

44. Because off-label uses are so common, information about those off-label uses, especially information concerning dosing, administration, effectiveness, and safety, is critically important to health care providers. Without access to this information, their patients may be deprived of significant health benefits and may even incur harm. "[P]ublic health can be served when health care professionals receive truthful and non-misleading scientific and medical information on unapproved uses." FDA, *Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices* 6 (2009);

see also FDA, *Draft Guidance for Industry: Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices* 6 (Feb. 2014) ("Revised Reprint Guidance") (recognizing the "value to health care professionals of truthful and non-misleading scientific or medical publications on unapproved new uses").

FDA Regulations Restrict Manufacturer Truthful, Non-Misleading Speech About Lawful Uses

45. Through its regulations and policies, FDA has asserted jurisdiction to regulate a wide swath of manufacturer speech and has imposed severe restrictions on what manufacturers may say about lawful uses of their drugs, both "on" and "off" label, and irrespective of whether the speech is truthful and non-misleading. These regulations and policies in many ways run counter to the FDCA's straightforward textual provisions, which allow manufacturers to market and promote an approved prescription drug to the full scope of its approval, and also omit any direct prohibition on off-label promotion. *See Caronia*, 703 F.3d at 154 ("The FDCA and its accompanying regulations do not expressly prohibit the 'promotion' or 'marketing' of drugs for off-label use."); *Amarin Pharma, Inc. v. FDA*, No. 1:2015cv03588, slip op. at 9 (S.D.N.Y. May 7, 2015).

Off-Label Uses in Prescription Drug Labeling or Advertising

46. The FDCA prohibits manufacturers from introducing or delivering "misbranded" drugs into interstate commerce. 21 U.S.C. § 331(a). A drug is misbranded if, for example, its "labeling is false or misleading in any particular," *id.* § 352(a), or if its labeling lacks "adequate directions for use," *id.* § 352(f). In addition, a prescription drug is deemed misbranded if its advertising fails to include "a true statement" of "such . . . information in brief summary relating to the side effects, contraindications, and effectiveness" as are required by FDA regulations. *Id.* § 352(n).

47. The FDCA defines "labeling" to mean "all labels and other written, printed or graphic matter (1) upon any article or its containers or wrappers, or (2) accompanying such article," 21 U.S.C. § 321(m), and "label" to mean "a display of written, printed, or graphic matter upon the immediate container of any article." *Id.* § 321(k). The Supreme Court has clarified that not all written, printed, or graphic matter that mentions a drug qualifies as "labeling." Instead, such matter may properly be considered as "accompanying" a drug when it has the same origin and same destination, is part of an integrated transaction, and constitutes an "essential supplement" to the drug. *See Kordel v. United States*, 335 U.S. 345, 348-50 (1948).

48. FDA has, through its regulations and policies, broadly defined labeling to include a wide assortment of written, printed, or graphic matter associated with a product, in a way that extends far beyond the FDCA itself. The relevant FDA regulation, for example, states in plain terms that a variety of materials—including "[b]rochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films . . . sound recordings, exhibits, literature, and reprints and similar pieces of printed audio or visual matter descriptive of a drug and references published (for example, the 'Physicians Desk Reference') for use by medical practitioners, pharmacists, or nurses, containing drug information supplied by the manufacturer, packer, or distributor"—are "hereby determined to be labeling" as defined in the FDCA. 21 C.F.R. § 202.1(*l*)(2).

49. In guidance documents and enforcement letters, moreover, FDA has asserted that reference texts, posts on social media, and communications between a manufacturer and a payer's formulary committee are deemed "labeling" subject to FDA's regulatory restrictions. *See*

FDA, Revised Reprint Guidance 10.[3] FDA has even gone so far as to interpret oral statements to constitute either advertising or labeling.[4]

50. This redefinition of "labeling" results in a broad criminalization of speech in part due to its effect on a different section of the FDCA. Under § 201(p) and § 505(a) of the statute, if a drug's "labeling" "prescribe[s], recommend[s], or suggest[s]" a new use for the drug—*i.e.*, one not indicated in the approved NDA—the drug then constitutes a "new drug" for which the manufacturer must seek a separate FDA approval. Introduction of the "new drug" into interstate commerce without this required approval constitutes a criminal offense. 21 U.S.C. § 331(d). Thus, a manufacturer's distribution of any material that falls under FDA's broad definition of "labeling" and that so much as "suggest[s]" an off-label use for its drug potentially subjects the manufacturer to criminal liability.

51. Additionally, under the misbranding provisions at 21 U.S.C. § 352(a), a manufacturer is prohibited from making "false or misleading" statements in labeling. This prohibition is consistent with established judicial precedent concerning commercial speech, *see, e.g.*, *Central Hudson Gas & Electric Corp. v. Public Service Commission*, 447 U.S. 557, 564 (1980), and by itself would be relatively uncontroversial. FDA, however, has argued that

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[3] *See* FDA, Center for Drug Evaluation and Research, DDMAC, Current Issues and Procedures, at 4 (Apr. 1994) (noting that "[f]ormulary 'kits' or other similar materials . . . that discuss a regulated product and that are prepared for and disseminated to hospitals, managed health care organizations, buying groups, and other institutions are promotional labeling"); *see also*, *e.g.*, FDA Warning Letter from Thomas Abrams, Dir., DDMAC, to Frank Baldino, Jr., Cephalon, Inc. (Feb. 27, 2007) (on file with FDA) (finding that a "promotional piece distributed . . . to the Maryland Department of Health and Mental Hygiene's Pharmacy and Therapeutics Committee" constituted labeling and, because of its claims, was misleading, thus rendering the medication "misbranded" under the FDCA); FDA Untitled Letter from Karen Rulli, DDMAC, to Lisa Drucker, Novartis Pharmaceuticals Corp. (July 29, 2010) (alleging that content posted by the company on Facebook was labeling, and that because it was false or misleading, misbranded the product).

[4] *See, e.g.*, FDA Letter from Mathilda Fienkeng, Regulatory Review Officer, DDMAC, to John Driscoll, S. Mng., Regulatory Affairs, Forest Labs. (Apr. 28, 2011) (addressing oral statements made by sales representatives); FDA Letter from Carole C. Broadnax, Regulatory Review Officer, DDMAC, to Stacey Tosadori, Dir., Regulatory Affairs, Amgen, Inc. (May 13, 2010) (addressing oral statements made by Amgen representative).

§ 352(a) of the FDCA means that "any and all scientific claims about the safety, effectiveness, contraindications, side effects, and the like regarding prescription drugs are presumptively untruthful and misleading," *unless* they satisfy the exceptionally high "substantial evidence" standard (the standard for approving a new drug), 21 C.F.R. § 202.1(e)(4)(ii)(b), (e)(6)(i)-(ii), or FDA has reviewed and approved them in advance—even if those claims are demonstrably true. *See Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 67 (D.D.C. 1998), *vacated as moot on other grounds sub. nom. Wash. Legal Found. v. Henney*, 202 F.3d 331, 333 (D.C. Cir. 2000).[5] This is because, in FDA's view, "health claims that have not been FDA approved are inherently misleading." *Friedman*, 13 F. Supp. 2d at 67. FDA thus has effectively appointed itself as the ultimate arbiter of what manufacturers can and cannot say about their products, requiring that promotional communications be limited to uses explicitly described in a drug's approved labeling and even then, be supported by FDA's "substantial evidence" standard. *See id.* ("In asserting that any and all scientific claims about the safety, effectiveness, contraindications, side effects, and the like regarding prescription drugs are presumptively untruthful or misleading until the FDA has had the opportunity to evaluate them, FDA exaggerates its overall place in the universe.").

52. Under the FDCA, "misbrand[ing]" also occurs if a drug's labeling does not bear "adequate directions for use." 21 U.S.C. § 352(f). The Act does not define "adequate directions for use," but FDA has defined that phrase to mean "directions under which a layman can use a drug safely and for the purposes for which it is intended." 21 C.F.R. § 201.5. Recognizing

[5] Although the "substantial evidence" standard for any claims or comparisons appears in a regulation addressed to "advertising," adopted under the Secretary's authority to require a short "true statement" in such advertising, 21 U.S.C. § 352(n), FDA applies the standard as well to so-called "labeling." *See, e.g.*, FDA Warning Letter from Andrew Haffer, OPDP, to Samuel Waksal, Kadmon Pharmaceuticals, Inc. (Nov. 28, 2013) (stating that a letter sent from the company to doctors constituted misbranding under 21 U.S.C. § 352(a) in part because it made claims for a specific patient population that were not supported by substantial evidence).

physicians' role as "learned intermediaries" who make educated medical decisions based on information from a variety of sources beyond a label, Congress exempted prescription drugs from the "adequate directions for use" requirement. 21 U.S.C. § 353(b)(4).

53. Uncomfortable with the prospect of doctors and drug companies communicating without FDA supervision, however, FDA has largely excised the prescription drug exemption from the statute. By regulation, FDA exempts prescription drugs from the "adequate directions for use" requirement *only if* the product labeling has "adequate information"—including the indications, effects, dosages, routes, methods, frequency and duration of administration, and any relevant hazards, contraindications, side effects, and precautions associated with the drug—to instruct medical professionals on how to use the product safely and for "the purposes for which it is intended." 21 C.F.R. § 201.100(c)(1). The regulations further provide that a drug's "intended use" is any use "for which it is advertised or represented," *id.*, regardless of whether such use is mentioned on the drug's label.

54. FDA's regulations effectively create a Catch-22 for pharmaceutical manufacturers. On one hand, manufacturers are *required* to include in product labeling detailed information about all intended uses, including those that are off-label, to avoid a misbranding charge based on a lack of "adequate directions for use." On the other hand, under the "new drug" rationale described above, manufacturers are *prohibited* from supplementing or revising the product labeling without FDA approval. FDA relies on this construct, which does not appear in the FDCA, to restrict pharmaceutical manufacturers such as Pacira from conveying to sophisticated health care professionals virtually any information—regardless of its quality or veracity—that differs from the FDA-approved product labeling or that is not supported by evidence meeting FDA's strict "substantial evidence" standard.

55. FDA has also used its regulations to impose an even more explicit prohibition against discussing "off-label" uses. Ironically, FDA claims authority for this prohibition on disclosing information pursuant to a statutory provision that *requires* disclosure. The FDCA empowers FDA to ensure that advertisements contain certain disclosures to facilitate prescribing decisions. The statute requires manufacturers to disclose certain information related to the established name of the drug, as well as information related to side effects, contraindications, and effectiveness; direct-to-consumer advertisements must also provide the audience with information on reporting adverse events to FDA. 21 U.S.C. § 352(n). FDA has, however, converted Congress's requirement of *more* manufacturer speech into an agency *restriction* on manufacturer speech. Specifically, 21 C.F.R. § 202.1(e)(4)(i)(a) provides that a prescription drug is misbranded if any advertisement for it "recommend[s] or suggest[s] any use that is not in the labeling accepted in [the drug's] approved new-drug application." Through its application of this regulatory provision, which FDA also applies to "labeling," *see supra* note 5, FDA bars manufacturer communications about prescription drugs that reference off-label uses. The accuracy, quality, and value of that information are wholly irrelevant to the analysis, under FDA's regulations.

56. In sum, FDA's construction of the FDCA—particularly its "new drug" and "misbranding" provisions—broadly prohibits manufacturers from discussing off-label uses in advertising or labeling. Because FDA has advanced such an exceedingly expansive view of which communications are subject to its jurisdiction, moreover, manufacturers are left with little room to convey truthful and non-misleading off-label information, regardless of its potential value to prescribers and the patients they serve.

FDA's "Safe Harbors" for Off-Label Speech

57. FDA has over the years articulated narrow, ill-defined exceptions to the general prohibition against manufacturer communication of off-label uses. These so-called "safe harbors" for non-promotional communications were developed, in large part, due to FDA's understanding that off-label use is not only lawful, but is a critical component of serving the public health. *See, e.g.*, Revised Reprint Guidance 6-7 (acknowledging the "value to health care professionals of truthful and non-misleading scientific or medical publications on unapproved uses"); *see also, e.g.*, *Legal Status of Approved Labeling For Prescription Drugs; Prescribing For Uses Unapproved By The Food And Drug Administration*, 37 Fed. Reg. 16,503, 16,504 (Aug. 15, 1972) ("The physician is [] responsible for making the final judgment as to which, if any, of the available drugs his patient will receive in light of the information contained in their labeling and other adequate scientific data available to him."). Despite FDA's repeated statements regarding the importance of off-label use and manufacturer dissemination of information relating to such use, and as highlighted by the examples provided herein, the Agency has not outlined a sufficiently clear regulatory pathway for manufacturers to engage in full and frank discussions with physicians about uses that are not explicitly described in the FDA-approved labeling.

58. An FDA regulation governing investigational (*i.e.*, unapproved) drugs, for example, prohibits manufacturers from representing "in a promotional context" that a drug is safe or effective prior to FDA approval, but makes clear that the provision "is not intended to restrict the full exchange of scientific information concerning the drug." 21 C.F.R. § 312.7. The contours of this "scientific exchange" exception have never been elucidated by the Agency in any binding or meaningful way, but FDA has made clear that the exception permits

manufacturers to make off-label statements only if they are non-promotional, objective, and do not draw conclusions about the safety or effectiveness of the off-label data. *See Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Treatment Use and Sale*, 52 Fed. Reg. 19,466 (May 22, 1987).

59. Similarly, FDA has stated in a non-binding, draft guidance document[6] that pharmaceutical manufacturers may respond to "unsolicited requests" for off-label information from health care professionals in limited circumstances. *See* FDA, *Draft Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices* (Dec. 2011). FDA has indicated that manufacturers may avail themselves of this safe harbor only if the request is not prompted "in any way" by the company and lays out specific parameters that a request should meet before being considered "unsolicited." *Id.* at 3. Among other criteria, this draft guidance also suggests that manufacturer responses should not be "promotional in tone or presentation," should be provided only in a "one-on-one" communication, and should not be provided by sales representatives or other commercial personnel. *Id.* at 10-15. The Agency's policy does not permit manufacturers to initiate off-label discussions, irrespective of whether the information shared is truthful and non-misleading, nor does it permit manufacturers and physicians to engage in a free-flowing conversation about off-label uses.

60. Finally, although FDA allows manufacturers to disseminate reprints of peer-reviewed scientific and medical publications, reference texts, and clinical practice guidelines that refer to off-label uses, it does so only when a number of rigorous criteria are met. *See* FDA,

[6] FDA typically "regulates" through issuing non-binding guidance documents in draft form, which are never finalized. This practice enables FDA to avoid responding to public comments. It also prevents regulated entities from being able to rely on the guidance, because the Agency considers itself free to disregard it at any point for any reason.

Revised Reprint Guidance. In particular, FDA states that manufacturers may lose the protection of the safe harbor simply by distributing off-label information in connection with other information that is "promotional in nature." *Id*. at 8.

61. As the examples above demonstrate, even FDA's purported "safe harbors" for off-label communication severely constrain manufacturers' ability to share truthful and non-misleading off-label information.

FDA's Limits on On-Label Communications

62. FDA also restricts truthful and non-misleading manufacturer speech about FDA-approved uses that the Agency acknowledges to be "on-label." Under FDA regulations governing promotional communications, the Agency presumes that manufacturer speech is "false or misleading" unless it meets the rigorous "substantial evidence" standard. 21 C.F.R. § 202.1(e)(6)(i)-(ii). The substantial evidence standard appears in the FDCA, where it was intended to serve as an appropriately high bar for obtaining market approval of an NDA; in other words, before a manufacturer may *sell* a drug, it must demonstrate to FDA that adequate and well-controlled investigations support the drug's safe and effective use. 21 U.S.C. § 355(d). The statute does not, however, authorize FDA to require substantial evidence before a manufacturer may *speak* about a drug that has already been approved. FDA nevertheless promulgated a regulation precisely to that effect and now routinely relies upon it to limit on-label speech.

63. One example arises in the area of product comparisons. Physicians regularly rely on scientific studies or other data that compare the safety or effectiveness of two or more products in order to select the treatment options that, in their medical judgment, are most appropriate for their patients. *See*, *e.g.*, Institute of Medicine, Initial Priorities for Comparative Effectiveness Research 29 (2009). Much of this research involves meta-analyses, observational

studies, or other "real world data"—which do not appear in the FDA-approved product labeling and which typically do not satisfy FDA's "substantial evidence" standard. Thus, as a general matter, pharmaceutical manufacturers may not disseminate meta-analyses, observational studies, or other clinically relevant "real world data" to physicians or any other health care stakeholders, despite the value of such information to making treatment decisions, because those types of information do not constitute "substantial evidence." *See* 21 C.F.R. § 202.1(e)(6)(i).

The Chilling Effect of the Government's Aggressive Enforcement Regime

64. Violations of the FDCA—including violations of its "new drug" and "misbranding" provisions—carry serious penalties. Introduction of a "misbranded" or unapproved "new" drug into interstate commerce is a criminal misdemeanor—and one for which the FDCA imposes strict liability. *See* 21 U.S.C. § 331, 333(a); *United States v. Park*, 421 U.S. 658, 680 (1975) (explaining that the FDCA "dispenses with the conventional requirement for criminal conduct—awareness of some wrongdoing"). A violation of the FDCA committed with "the intent to defraud or mislead" or after a prior conviction, on the other hand, is a felony. 21 U.S.C. § 333(a).

65. Any conviction under the FDCA—even for a misdemeanor—may also result in exclusion from participation in federal health care programs. Under 42 U.S.C. § 1320a-7(b), the Secretary of HHS may prohibit an individual or entity convicted of violating the FDCA from participating in any federal health care program if the violation "relat[ed] to fraud" and occurred in connection with a delivery of a health care item in a government program. If the conviction is for a felony offense relating to fraud in connection with the delivery of a health care item or service, exclusion is mandatory. 42 U.S.C. § 1320a-7(a)(3). To the extent that a particular "new drug" or "misbranding" violation falls within the scope of § 1320(a)-7, a conviction therefore

carries a risk of total exclusion from federal reimbursement. *See, e.g.*, *Friedman v. Sebelius*, 686 F.3d 813, 818-24 (D.C. Cir. 2012) (holding that a misdemeanor conviction for misbranding premised on strict liability can, at least under some circumstances, support exclusion under 42 U.S.C. § 1320a-7(b)). Due to the extraordinary power of these so-called administrative remedies to "kill" the company, they are often referred to as the "corporate death penalty."[7] And the return of an indictment alone can give rise to permissive exclusion, leading to a company seeing its reimbursement halted and "corporate death" before it gets a day in court.

66. Combined with FDA's expanded interpretation of the FDCA, these potential draconian consequences create a potent chilling effect on manufacturers' willingness to engage in truthful, non-misleading speech about the lawful use of their products.

Legal Requirements for FDA to Modify Approval or Label

67. While FDA imposes rigorous standards for label approval in the first instance, FDA may only revise, amend, or otherwise order changes to a product's label post-approval under very limited circumstances and only if the Agency observes designated procedures.

68. In order to initiate the procedures for revising a drug's approved label, FDA must typically identify "new safety information." 21 U.S.C. §§ 355(o)(4)(A), 355-1(a)(2)(A). "New safety information" means "information derived from a clinical trial, an adverse event report, a postapproval study . . . or peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system under section 355(k) of [the FDCA]; or other scientific data deemed appropriate by the Secretary about . . . a serious risk or an unexpected serious risk associated with use of the drug that the Secretary has become aware of (that may be based on a

[7] Barry J. Pollack, *Time to Stop Living Vicariously: A Better Approach to Corporate Criminal Liability*, 46 Am. Crim. L. Rev. 1393, 1403 (2009); *see United States v. Stein*, 435 F. Supp. 2d 330, 381-82 (S.D.N.Y. 2006) (noting that indictment is often a matter of "life and death" to companies).

new analysis of existing information) since the drug was approved." *Id.* §§ 355-1(b)(3), 355(o)(2)(C).

69. If FDA believes a labeling change is necessary to protect the public health, the Agency must make a formal determination to that effect and must provide notice to the NDA holder, allowing it ample time to submit proposed labeling changes or to challenge FDA's determination under the respective statutory framework. 21 U.S.C. § 355(o)(4)(B) (stating that following notification, an NDA holder may respond with an explanation for why it believes a labeling change is not warranted); *see*, *e.g.*, *id.* § 355(o)(4)(F) (stating that, after receiving a safety labeling change order from FDA, the NDA holder "may appeal using dispute resolution procedures established by [FDA] in regulations and guidance").

70. Similarly, if FDA seeks to withdraw approval of an NDA entirely, it may only do so under certain factual circumstances, the majority of which concern the safety or effectiveness of the drug. 21 U.S.C. § 355(e); 21 C.F.R. § 314.150(b)(3). In all instances, including where there is an "imminent hazard to the public health," FDA must afford the NDA holder due notice and opportunity for a hearing. 21 U.S.C. § 355(e); 21 C.F.R. § 314.150(b)(3).

71. There is no statutory or regulatory authority for FDA unilaterally to revise, amend, or order revisions to a product's approved label in the absence of new safety or effectiveness information or specific, enumerated failures on the part of the applicant. Nor does FDA have legal authority to use its enforcement powers to revise a product's approved label.

FACTUAL ALLEGATIONS

Pacira's Development of EXPAREL for General Postsurgical Analgesia

72. Pacira is a specialty pharmaceutical manufacturer focused on the clinical and commercial development of drug products that meet the needs of acute care practitioners and

their patients, for use primarily in hospitals and ambulatory surgery centers. Pacira's primary goal is to deliver non-opioid products for postsurgical pain control.

73. Pacira was founded in 2007, and is a former business unit of SkyePharma PLC. Prior to that, the company was known as Depotech Corporation. Pacira has one key product, EXPAREL (bupivacaine liposome injectable suspension).[8] Pacira and its predecessor companies have worked to develop the innovative technology behind EXPAREL for 21 years, and have invested $500 million in this endeavor.

74. EXPAREL is a non-opioid local analgesic to control postsurgical pain. It combines bupivacaine, a local anesthetic that has been marketed in the United States continuously since 1972, when FDA first approved the drug, with Pacira's DepoFoam drug delivery platform. EXPAREL is administered by infiltration "into the surgical site." EXPAREL Prescribing Information ("PI"). Bupivacaine, the active ingredient in EXPAREL, is a well-known anesthetic with a long and safe history that FDA has approved for many uses. For example, the "Indications and Usage" section for MARCAINE (bupivacaine), states that it is approved for use broadly for "the production of local or regional anesthesia or analgesia for surgery, dental and oral surgery procedures, diagnostic and therapeutic procedures, and for obstetrical procedures." And MARCAINE's "Dosage and Administration" section states generally that "[f]or specific techniques and procedures, refer to standard textbooks," rather than spelling out in detail how this local anesthetic is to be administered.

75. DepoFoam is a multivesicular liposome technology that encapsulates drugs without altering their molecular structure and then releases them over a desired time period. DepoFoam is a proprietary drug delivery technology and a key component of Pacira's product,

[8] Pacira also manufactures another product, DEPOCYT (cytarabine liposome injection), which is approved to treat lymphomatous meningitis, because no other manufacturer is equipped to do so.

EXPAREL. DepoFoam is made up of liposomes, which are spherical composite particles of lipid bilayers. EXPAREL is composed of many independent liposomes, and each liposome's lipid bilayer encapsulates an interior aqueous chamber that contains bupivacaine. The lipid membranes in each liposome of the DepoFoam material protect the contents of the interior chambers from seeping out.

76. After EXPAREL is infiltrated into the surgical site via injection, over time the liposomes break down (as intended), and the bupivacaine gradually diffuses into the soft tissue. Once in the soft tissue, the bupivacaine comes into contact with compromised nerves and exerts a local analgesic effect. Typically, one dose of EXPAREL will fully release its stores of bupivacaine 48 to 110 hours following injection into the surgical site. The combination of DepoFoam with bupivacaine results in a delayed release of bupivacaine that allows patients to experience the effects of the drug for a longer period of time than they otherwise would if the bupivacaine alone were injected.

77. Unlike a typical injection of fluid that immediately and widely diffuses into the soft tissue, EXPAREL can be injected with directional precision because it tends to remain at or near the site of injection. Surgeons and other health care providers can aim the drug such that it is injected in close proximity to a surgical site, thereby affording patients targeted relief from postsurgical pain.

Pacira's Successful Clinical Trials Demonstrate EXPAREL's Safety and Efficacy in Postsurgical Analgesia

78. Pain is one of the most challenging areas of medicine to study effectively. "Pain scores" are inherently subjective patient-reported outcomes, and it is difficult to measure the effect of medications on these scores. In addition, for ethical reasons, subjects in studies of pain

medicines cannot be allowed to suffer in pain and so must be provided relief with "rescue" pain medications, usually opioids, creating still further complications in data analysis.

79. In light of these challenges, scientists and doctors concur that the best way to design clinical studies for certain types of pain medications is to extrapolate from clinical studies in certain areas. For example, studies may be conducted in one soft tissue (or non-orthopedic) setting and in one hard tissue (or orthopedic) setting, which represent opposite ends of the spectrum of human anatomy and would thus be expected to reflect the range of different potential clinical applications. Scientists and doctors find it appropriate to extrapolate from two such trials to conclude that the drug is generally safe and effective to treat pain.

80. To determine whether extrapolation is appropriate, as a general matter, scientists, doctors, and FDA itself consider two principal factors: (1) the pain itself, which is characterized by a number of features, including duration, pattern of occurrence, intensity, and cause; and (2) the drug's mechanism of action. First are the characteristics of the pain. If, for example, the pain to be treated is caused by trauma to the skin or the underlying tissue because of a surgical incision, as with postsurgical pain, then the same pain control medication will address that root source of pain regardless of where it occurs. In a similar fashion, if the pain to be treated is caused by a muscle ache, then the same pain control mechanisms (*e.g.*, acetaminophen or ibuprofen) can provide pain relief whether those muscles are in the leg, the back, or the neck. Thus, the features of the pain, rather than its location on or within the body, are the relevant consideration. Second is the drug itself, and in particular, its mechanism of action and pharmacodynamic properties. As FDA has explained, "whether the finding of analgesia should be replicated in specific patient populations (*i.e.*, subjects with particular types of pain) versus across patient populations depends on how much is known about the pharmacology of the drug

under development." FDA, *Draft Guidance for Industry: Analgesic Indications: Developing Drugs and Biological Products* 7 (Feb. 2014) ("FDA Analgesic Guidance").

81. FDA itself recognizes that "[a]ll analgesics have characteristics that create a challenge for clinical trial design." FDA Analgesic Guidance at 15. As a result, FDA has a long history of approving drugs for broad analgesic indications based on clinical trials in more limited subpopulations.[9] For example, FDA has stated that for "general acute pain indications," meaning for pain requiring treatment for no more than a few weeks, two "successful trials in nociceptive pain, one in visceral pain and one in nonvisceral pain, generally will be considered adequate." *Id.* at 2, 5. That is, in FDA's view, two successful trials are sufficient to support a "*general*" pain indication for *all* types of acute pain, *i.e.*, an even broader indication than the "post-surgical" pain indication that Pacira sought (and received).

82. FDA's views, as reflected in its 2014 guidance regarding analgesics, are not new. FDA has favored extrapolation and broad indications for analgesic medications wherever appropriate. A 1992 version of the guidance stated that "[e]vidence that an agent has analgesic activity in pain of several different etiologies will justify 'general purpose' analgesic labeling unless special considerations indicate that this is not appropriate." FDA, *Guidance for Industry: Guideline for the Clinical Evaluation of Analgesic Drugs* 22 (Dec. 1992). In FDA's view, if an analgesic is demonstrated to be safe and effective for a specific type of pain, in the absence of safety concerns weighing against extrapolation, then it should be approved with as broad an indication as possible.

83. Bob Rappaport, the then-Director of the Division of Anesthesia, Analgesia, and Addiction Products at the Center for Drug Evaluation and Research, gave a presentation on

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[9] *See, e.g.*, Bob A. Rappaport, M.D., Overview of the August 19, 2010 ALSDAC Meeting to Discuss NDA-22-516 for Cymbalta for the Treatment of Chronic Pain (July 26, 2010).

March 15, 2012 entitled "Regulatory Issues Related to the Development of Drugs to Treat Painful Peripheral Neuropathy."[10] This presentation explained FDA's views regarding pain medications and the indications that should be granted.

84. In this presentation, Rappaport stated that indications, or "[t]he specific condition or use the product has been approved for," may be broad (such as "for the treatment of pain") or narrow (such as "for the management of the pain of diabetic peripheral neuropathy"). Rappaport Presentation at 3. He further explained that a broad indication could be extrapolated from a trial in a narrower clinical setting: while "[s]ubjects must represent the appropriate patient population," "[i]n some cases, extrapolation of safety and/or efficacy data may be allowed, resulting in approval based on [a] single trial or smaller number of subjects." *Id.* at 4-5. Although extrapolation is decided on a case-by-case basis during the NDA process, Rappaport stressed the benefits of extrapolation, noting that we "[n]eed to have analgesics with broader indications." *Id.* at 10.

85. Consistent with its own guidance and policy, and scientific and medical understandings, FDA has in the ordinary course approved pain drugs for general pain indications by extrapolating safety and effectiveness from data derived from studies of specific types of pain. For example, FDA approved NUCYNTA (tapentadol) for the relief of "moderate to severe acute pain" on the basis of one clinical study in bunionectomy and one in end-stage osteoarthritis of the hip or knee, and approved OFIRMEV (intravenous acetaminophen) for mild to moderate pain on the basis of one study in abdominal lapraroscopic surgery and one in total hip or knee replacement.

[10] Bob A. Rappaport, M.D., *Regulatory Issues Related to the Development of Drugs to Treat Painful Peripheral Neuropathy*, Presentation at the 2012 Foundation for Peripheral Neuropathy National Research Symposium (Mar. 15, 2012) ("Rappaport Presentation"), http://www.acttion.org/static/docs/Rappaport_slide_presentation.pdf.

86. In light of these understandings shared by pain scientists, doctors, and regulatory experts, Pacira understood that it could obtain a broad approval and indication for use of EXPAREL in surgical sites generally based on one trial involving hard tissue or orthopedic pain (patients undergoing bunionectomies) and one trial involving soft tissue pain (patients undergoing hemorrhoidectomies).

87. This understanding was bolstered by the fact that in 1972, FDA approved bupivacaine with an indication that included, among other things, local analgesia for surgery. Because bupivacaine is the active ingredient in EXPAREL and was previously approved by FDA, Pacira was permitted to submit the EXPAREL NDA through an abbreviated regulatory pathway, the so-called § 505(b)(2) NDA. The 505(b)(2) pathway allowed Pacira to rely, in part, on FDA's previous finding of safety and effectiveness for bupivacaine to support approval of EXPAREL. 21 U.S.C. § 355(b)(2).

88. Pacira's clinical trial involving bunionectomies evaluated the safety and efficacy of 106 mg of EXPAREL versus placebo in 193 patients. EXPAREL was administered directly into the surgical site at the conclusion of surgery, and pain intensity was rated by the patients on a 0 to 10 numeric rating scale at multiple time points through 72 hours. The primary endpoint was the area under the curve of pain intensity scores collected over the first 24-hour period. EXPAREL met the primary endpoint, demonstrating a significant reduction in pain intensity compared to placebo at 24 hours.

89. The clinical trial involving hemorrhoidectomies evaluated the safety and efficacy of 266 mg EXPAREL versus placebo in 189 patients. EXPAREL was administered directly into the surgical site at the conclusion of surgery, and pain intensity was rated by the patients on a 0 to 10 numeric rating scale at multiple time points up to 72 hours. The primary endpoint for this

study was the area under the curve of pain intensity scores collected *over the first 72-hour period*. EXPAREL met the primary endpoint of this study as well, demonstrating a statistically significant reduction in pain intensity compared to placebo through 72 hours.

90. Critically, in this study, test subjects given placebo relied on more opioid "rescue medication" than did subjects given EXPAREL. The study showed with a high degree of statistical significance that 28% of patients receiving EXPAREL did not require rescue pain medication through 72 hours compared to only 10% of patients receiving placebo ($p<0.0001$).

91. As a matter of science and medicine, EXPAREL's mechanism of providing pain relief, and its demonstrated safety and effectiveness in bunionectomy and hemorrhoidectomy, establish that it would be generally safe and effective in controlling postsurgical pain. EXPAREL works by releasing bupivacaine over an extended period of time. Bupivacaine, in turn, exerts its anesthetic effect when it comes in contact with nerve cells where it blocks sodium channels and prevents the initiation and transmission of nerve impulses, effectively impeding the generation and conduction of pain from the nerves near where it is placed. The mechanism of action is the same whether the nerves upon which EXPAREL acts are located in the toe, the anus, the knee, the abdomen, the breast, or any other site of the body. There is no reason to expect that EXPAREL's analgesic effect would differ when administered in connection with surgeries other than bunionectomies and hemorrhoidectomies.

92. In the case of EXPAREL, extrapolation is particularly appropriate because Pacira's clinical trials were conducted in bunionectomy and hemorrhoidectomy—surgeries involving parts of the anatomy with radically different features. In the hemorrhoidectomy study, EXPAREL was demonstrated to be safe and effective at controlling pain in a part of the body that consists entirely of soft tissue. EXPAREL was also proven safe and effective at controlling

the pain associated with bunionectomy—a surgical procedure in a party of the body consisting primarily of bone and joint (and very little soft tissue). Furthermore, because the active ingredient in EXPAREL, bupivacaine, exerts its analgesic effect by preventing transmission of nerve impulses, it can be expected to have a similar effect on nerves anywhere in the body. The safety and effectiveness of EXPAREL in these two surgical models combined with bupivacaine's recognized mechanism of action provides a clear scientific and medical rationale for concluding that EXPAREL's clinical benefits are generalizable to other surgical sites.

FDA Approves EXPAREL with a Broad Indication for Postsurgical Analgesia

93. On September 28, 2010, Pacira submitted its NDA for EXPAREL under § 505(b)(2) of the FDCA. The NDA referenced FDA's prior approval for MARCAINE (bupivacaine hydrochloride injection), and sought approval of EXPAREL for general use in relieving postsurgical pain.

94. The NDA was accompanied by a proposed PI, which included sections titled: "Indications and Usage," "Warnings and Precautions," "Dosage and Administration," and "Clinical Studies." Specifically, the proposed Indications and Usage section stated that EXPAREL is indicated to "produce postsurgical analgesia." The proposed Warnings and Precautions section contained no warnings against the use of EXPAREL in surgical procedures outside of bunionectomy and hemorrhoidectomy.

95. FDA conducted a thorough review of the application.

96. FDA Medical Officer Dr. Arthur Simone prepared a "Medical Review," noting the broad scope of the indication and dosing regimen proposed by Pacira. Dr. Simone recommended narrowing the Indications and Usage section of the PI to state that EXPAREL was approved only for "postoperative analgesia following hemorrhoidectomy and bunionectomy,"

but FDA elected not to adopt this limitation. During negotiation of the PI, FDA also proposed including a sentence in the Warnings and Precautions section stating that "EXPAREL has been determined to be effective for providing postoperative analgesia only for bunionectomy and hemorrhoidectomy procedures; it is not recommended for use following other surgical procedures as its safety and efficacy have not been evaluated," but that was not adopted either.

97. FDA approved Pacira's NDA on October 28, 2011. In so doing, FDA rejected Dr. Simone's proposed limitation to the Indications and Usage section and abandoned its proposal to include limiting language in the Warnings and Precautions section of the label. Had FDA so desired, it could have easily limited the breadth of the approved indication for EXPAREL, as it has done for other pain medications such as DEPODUR (indicated for "treatment of pain following major surgery") and VICOPROFEN (indicated for "short-term . . . management of acute pain" and "is not indicated for the treatment of such conditions as osteoarthritis or rheumatoid arthritis"). Instead, after due consideration, FDA approved EXPAREL with an indication of "postsurgical analgesia," as originally proposed by Pacira. The final, approved form of the Indications and Usage section of the PI states that "EXPAREL is . . . indicated for administration into the surgical site to produce postsurgical analgesia," with no limitations on the surgical site. Under FDA's regulations, the breadth of a drug's approved indication is controlled by the "Indications and Usage" section and the "Contraindications" section of the FDA-approved PI. *See* 21 C.F.R. § 201.57(c)(2). The Indications and Usage section for EXPAREL does include a limitation: "EXPAREL has not been studied for use in patients younger than 18 years of age." Thus, while FDA rejected the suggestion of its medical reviewer to impose a limitation on the type of surgery for which the drug is approved for use, it did include a limitation against use in pediatric patients.

98. The final, approved form of the Dosage and Administration section of the PI first states that "[t]he recommended dose of EXPAREL is based on the surgical site and the volume required to cover the area." As with MARCAINE, *see supra* ¶ 74, the PI thus necessarily contemplates that physicians will use their medical judgment when administering EXPAREL in different surgical sites, and such judgment is necessary and appropriate in the context of administering local anesthetics during surgery. Because the EXPAREL PI goes on to provide a dosing range based on specific dosing recommendations for hemorrhoidectomies and bunionectomies, the inclusion of a general dosing instruction (dosing based on the surgical site and volume required for the area) would be entirely unnecessary if the approved indication were limited to hemorrhoidectomies and bunionectomies. Moreover, inclusion of specific doses in the "Dosage and Administration" section does not control or otherwise limit the indication provided in the "Indications and Usage" section because the breadth of a drug's *indication* is controlled by the "Indications and Usage" section (and the "Contra*indications*" section).

99. The final, approved form of the Clinical Studies section of the PI states that: "The efficacy of EXPAREL was compared to placebo in two multicenter, randomized, doubleblinded clinical trials. One trial evaluated the treatments in patients undergoing bunionectomy; the other trial evaluated the treatments in patients undergoing hemorrhoidectomy." While noting that "EXPAREL has not been demonstrated to be safe and effective in other procedures," the Clinical Studies section does not purport to limit the general "postsurgical analgesia" indication found in the Indications and Usage section of the label or recommend against use in surgical sites other than bunionectomy and hemorrhoidectomy.

100. In addition, if FDA had intended to approve EXPAREL for use in controlling postsurgical pain arising only from bunionectomies and hemorrhoidectomies, FDA would have

required that Pacira conduct two studies of EXPAREL in bunionectomies and also two studies of EXPAREL in hemorrhoidectomies, for a total of four pivotal studies.

101. FDA's application of the Pediatric Research Equity Act ("PREA") to EXPAREL further demonstrates EXPAREL's approval for general use in managing "postsurgical analgesia." PREA requires the conduct of pediatric clinical studies for certain drugs. 21 U.S.C. § 355c. Specifically, it requires NDA sponsors to submit data from pediatric clinical studies that are adequate to assess the safety and effectiveness and support dosing and administration for pediatric populations. *Id.* § 355c(a)(2)(A).

102. The text of PREA, its legislative history, and FDA guidance interpreting PREA all make clear that FDA's authority to require pediatric clinical studies is limited to studies of approved, or on-label, indications of a drug. 21 U.S.C. § 355c(a)(2)(A) (stating that the data must be adequate "to assess the safety and effectiveness of the drug . . . for the *claimed indications*") (emphasis added); S. Rep. 108-84, at 6-7 (2003) (explaining that Congress established "clear limitations" in PREA such that pediatric assessments were only required for a drug's "claimed indications"); FDA, *Draft Guidance for Industry: How to Comply with the Pediatric Research Equity Act* 14 (Sept. 2005) ("Under PREA . . . a pediatric assessment is required only on those indications included in the pending [drug] application"); FDA, *Retrospective Review of Information Submitted and Actions Taken in Response to PREA* 11 (2003) ("PREA requires studies only in the specific indications for which the triggering application is approved. . . . For example, under PREA a product approved for the treatment of chronic myeloid leukemia in adults might have the potential for activity against neuroblastoma in younger children, but studies *could not be required* as it is not the same indication as that in the application that triggered PREA.") (emphasis added).

103. Under PREA, FDA can waive studies in children if they are not necessary. According to FDA, pediatric studies would not be necessary, "for example, if the disease or condition for which the drug is being used in adults does not exist in children, such as prostate cancer," in which case "FDA would waive studies for children." Lynne Yao, M.D., *FDA takes step to encourage pediatric drug studies*, FDAVoice (Aug. 26, 2013) (FDA's official blog "brought to you from FDA's senior leadership and staff"), http://blogs.fda.gov/fdavoice/index.php/tag/pediatric-research-equity-act-prea/.

104. The FDA approval letter for EXPAREL expressly requires Pacira to conduct pediatric studies pursuant to PREA's requirements. *See* Letter from B. Rappaport to Pacira Pharmaceuticals, Inc. (Oct. 28, 2011) (describing, under the heading "REQUIRED PEDIATRIC ASSESSMENTS," four studies FDA is requiring Pacira to conduct in pediatric patients "undergoing multiple surgical procedures"). Neither bunions nor hemorrhoids, however, are childhood conditions, a fact FDA acknowledged in correspondence concerning the design of the pediatric studies. *See* FDA General Advice Letter from B. Rappaport to G. Knott (Nov. 20, 2012) (stating that neither hemorrhoidectomy nor bunionectomy "is commonly performed in any segment of the pediatric patient population").

105. Given that under PREA FDA may only require pediatric studies for on-label indications, and that bunionectomies and hemorrhoidectomies rarely occur in children and teenagers, the only way FDA could have reached a conclusion that pediatric studies were required for EXPAREL is if FDA understood the product's approved indication to broadly cover postsurgical pain relief.

106. FDA's understanding that EXPAREL's approval is not limited to bunionectomies and hemorrhoidectomies is further evidenced by correspondence between the Agency and Pacira

concerning the type of surgery in which the pediatric studies should be performed. On June 29, 2007 and in September 2010, prior to approval of EXPAREL, Pacira proposed pediatric studies in exploratory laparoscopy, genito-urinary surgery, and lower extremity orthopedic surgery. In January and September 2012, after approval of EXPAREL, Pacira proposed studies in pediatric patients "undergoing various surgical procedures," to which FDA's only objection was that such a study design would not be sufficient to capture enough data to determine the safety, efficacy, or dosing of EXPAREL "for any surgical procedure" in pediatric patients. In October 2013, and in response to that objection, Pacira proposed tonsillectomy studies to satisfy the PREA requirement. FDA responded on February 5, 2014 that the company should obtain pharmacokinetic data from use of EXPAREL in tonsillectomies in adults prior to conducting such studies. In June 2014, Pacira then submitted a protocol for an adult tonsillectomy study to FDA and began enrolling patients in that study, without objection from FDA.

107. At no point did FDA object to Pacira's proposals of pediatric laparoscopic, genito-urinary, lower extremity orthopedic, or tonsillectomy surgeries on the basis that such surgeries were outside the scope of EXPAREL's approved indication.

108. Furthermore, if—as claimed in the Warning Letter—FDA understood EXPAREL's approval to mean that there is insufficient information to demonstrate the product's safety and effectiveness in procedures other than hemorrhoidectomy or bunionectomy, it would raise serious ethical concerns to require Pacira to determine the safety and effectiveness of EXPAREL in such other procedures through clinical studies involving children rather than adults.

109. FDA's requirement that Pacira conduct pediatric studies of EXPAREL under PREA reinforces that FDA cannot credibly interpret the approved indication for EXPAREL to be limited to postsurgical analgesia only for bunions and hemorrhoids.

EXPAREL's Value to the Public Health

110. Pacira launched EXPAREL in April 2012 and from that time until the September 2014 Warning Letter has operated under the broad indication granted by FDA for EXPAREL. A wide range of physicians administer EXPAREL into the surgical site to produce postsurgical analgesia. Consistent with the indication, physicians use EXPAREL in a variety of surgical sites, not just bunionectomy and hemorrhoidectomy.

111. Physicians choose EXPAREL because it benefits their patients and improves public health. For many patients, postsurgical pain is significant and lasting. Lasting, significant pain may increase the length of a patient's hospital stay, which can place added stress on hospital staff and drive up the cost of health care. Post-operative pain can impair clinical outcomes (*i.e.*, it might lead to postsurgical complications) and induce chronic postsurgical pain syndromes. *See* John C. Rowlingson, Editorial, *We're on the Road to Depo-Local Anesthetics, But We Aren't There Yet*, 117(5) Anesthesia & Analgesia 1045, 1045 (Nov. 2013).

112. "Successful management of post surgical pain can have an impact on a patient's quality of life. Studies have shown that effective management of pain during the acute phase can have an influence on whether or not chronic pain develops." J. Hutchins et al., *Ultrasound guided subcostal transversus abdominis plane (TAP) infiltration with liposomal bupivacaine for patients undergoing robotic assisted hysterectomy: A prospective randomized controlled study*, 138 (3) Gynecol. Oncol. 609, 609 (2015).

113. Numerous surveys in recent decades have shown that "despite efforts to improve peri- and postsurgical analgesia, the incidence and severity of postsurgical pain have remained relatively unchanged over time." S. Cohen et al., *Liposome bupivacaine for improvement in economic outcomes and opioid burden in GI surgery: IMPROVE Study pooled analysis*, 2014(7) J. of Pain Research 359, 359 (June 2014).

114. EXPAREL has been used in more than 1.3 million patients since 2012 in a host of surgical procedures (both soft and hard tissue surgeries) including, among others: abdominal surgeries (*e.g.*, abdominoplasty); bariatric surgeries; bunionectomies; cesarean sections; colectomies (open and laparoscopic); gastrectomies; hemorrhoidectomies; hernia repair; hysterectomies; ileostomy reversals; joint replacements (*e.g.*, total knee arthroplasty; hip replacement procedures); nephrectomies; reconstructive and cosmetic plastic surgery; spinal procedures; and thoracic surgeries (*e.g.*, thoracotomies).

115. In particular, many health care providers regularly administer EXPAREL into the *transversus abdominis plane*, referred to as "iTAP" or "TAP."

EXPAREL's Value as an Opioid Alternative

116. EXPAREL addresses a critical unmet medical need for a non-opioid postsurgical analgesic.

117. Opioids, which are commonly prescribed to control postsurgical pain, are frequently associated with harmful side effects like dizziness, sedation, confusion, and respiratory depression. Opioids are known to trigger a range of adverse events in certain patients. These events range from the relatively minor, such as constipation, dry mouth, and low sex hormones, to the serious, including central sleep apnea, heart and lung problems, and accidental overdose or death.

118. In addition, doctors, advocacy groups, and other stakeholders (including the federal government) share a concern that patients who use opioids to relieve acute postsurgical pain may thereafter become addicted to or dependent on opioids.

119. In addition, prescription opioids have been identified as a major contributor to the current national addiction epidemic. *See* Office of National Drug Control Policy, *Fact Sheet: Opioid Abuse in the United States* (Feb. 11, 2014), https://www.whitehouse.gov/sites/default/files/ondcp/Fact_Sheets/opioids_fact_sheet.pdf.

120. EXPAREL holds value as an alternative to opioids, which assists in combatting the risks of overdose and other adverse events associated with opioids, including the potential for addiction.

121. Physicians can and do prescribe EXPAREL to control postsurgical pain at least in part because it reduces or, in some cases, eliminates the patient's consumption of opioids.

122. As an opioid-alternative, EXPAREL is especially valuable to the U.S. Department of Defense and members of the armed services. Members of the U.S. military requiring surgery in connection with battlefield injuries or otherwise want to stay alert and return to service as quickly as possible. Moreover, some senior officers fear that, under the influence of pain-relieving narcotics, they may inadvertently disclose classified military information and so prefer to avoid using opioids whenever possible. EXPAREL provides a valuable medical option for Department of Defense physicians and patients.

123. Since May 2013, when EXPAREL became available for use at the Naval Medical Center in San Diego, California, the drug has been incorporated into multi-modal analgesia regimens, resulting in clinical quality improvement. *See* Nicole M. King, LT., M.D. et al., *Retrospective Analysis of Quality Improvement When Using Liposome Bupivacaine for*

Postoperative Pain Control, Presented at American Society of Regional Anesthesia and Pain Medicine (ASRA); May 14-16, 2015 Las Vegas, Nevada. "Since liposome bupivacaine became available, there has been a noticeable decrease in the use of [continuous thoracic epidural]. Given the relative simplicity of administration and the seemingly comparable efficacy for postsurgical analgesia, liposome bupivacaine may be an excellent alternative to epidural anesthesia." *Id.*

124. EXPAREL has been administered successfully in a host of different surgical procedures at numerous military treatment facilities around the country, including Walter Reed National Military Medical Center in Maryland, the United States Naval Hospital Camp Le Jeune in North Carolina, and the United States Air Force David Grant Medical Center at Travis Air Force Base in California.

Other Values of EXPAREL

125. EXPAREL has an excellent safety record. Since Pacira launched the product in 2012, few adverse events have been reported. Pacira's post-marketing integrated safety analysis has identified only 455 adverse events following 1,300,000 exposures (0.035% rate of adverse events). Pacira's exceptional safety profile extends across different surgical sites in which the drug is administered. Neither its adverse event profile, nor that of bupivacaine (its active ingredient), suggests any safety concerns for use in surgical sites other than bunionectomy and hemorrhoidectomy.

126. EXPAREL also has important advantages that lead physicians to choose it over alternative non-opioid analgesic products for some patients.

127. EXPAREL is a local anesthetic that has the same active ingredient as MARCAINE (bupivacaine hydrochloride injection). MARCAINE was approved by FDA in

1972 and is indicated for the production of local or regional anesthesia or analgesia for surgery, dental and oral surgery procedures, diagnostic and therapeutic procedures, and for obstetrical procedures. *See* MARCAINE PI. Bupivacaine is the active ingredient in both EXPAREL and MARCAINE. What sets EXPAREL apart is its capacity to deliver bupivacaine in a controlled fashion over time, providing long-lasting relief with a single dose. Unlike MARCAINE, EXPAREL's liposomal formulation prevents the bupivacaine from diffusing away from the nerves in the surgical site and being absorbed in the bloodstream. In addition, at certain high doses, bupivacaine can be toxic. EXPAREL allows for bupivacaine to be released slowly into the body over a period of time.

128. Some physicians also choose to use EXPAREL rather than pain pumps, which are medical devices consisting of a reservoir of pain medication, such as bupivacaine, a catheter implanted into the body, and a pump that infuses the pain medication through the catheter to the affected area. For example, the ON-Q pump is an elastomeric infusion pump intended to provide continuous delivery of medication (such as local anesthetics) to or around surgical wound sites and/or close proximity to nerves, for preoperative, perioperative, and postoperative regional anesthesia and pain management.

129. Surgeons may prefer EXPAREL over ON-Q, which may require additional operating room time, and involve risk of infection, risk of device malfunction, and risk of migration or dislodgment of an indwelling catheter. Because of how it is administered, EXPAREL does not present catheter-related risks. EXPAREL also does not require elastomeric bags and PCA (Patient Controlled Analgesia) systems, which can introduce catheter-related issues.

130. ON-Q's manufacturer, Halyard Health, Inc., has made numerous unsupported superiority claims and misrepresentations about Pacira's product, EXPAREL. In particular, Halyard has distributed promotional materials suggesting that ON-Q is safer and more effective than EXPAREL.

131. Halyard's messaging has repeatedly attacked EXPAREL and Pacira's truthful, non-misleading claims concerning pain relief. Halyard has gone so far as to call EXPAREL, a drug that satisfied FDA's rigorous approval process, "snake oil" and "voodoo magic."

132. FDA's regulations prevent Pacira from responding to Halyard's unfounded statements because by their terms, those regulations require Pacira (but not Halyard) to support any comparative claims with FDA's high standard for "substantial evidence," namely, data from well-controlled and randomized head-to-head studies. 21 C.F.R. §§ 202.1(e)(6), 314.126(a).

Pacira's Truthful and Non-Misleading Speech About EXPAREL's Lawful Uses

133. Based on the label approved by FDA, Pacira initially felt free to provide truthful and non-misleading information to health care providers about EXPAREL's use in surgical sites other than bunionectomy and hemorrhoidectomy. For example, Pacira told physicians that EXPAREL is a liposome injection of bupivacaine indicated for administration into the surgical site to produce postsurgical analgesia. Pacira also discussed with physicians how EXPAREL could be used in specific surgical sites other than bunionectomy and hemorrhoidectomy to produce postsurgical analgesia. Pacira discussed with physicians the method of administering EXPAREL into the *transversus abdominis plane* (or iTAP) within the surgical site.

134. Pacira also provided physicians with written administration guides that memorialized the experiences of other physicians. Pacira developed and distributed educational technique guides representing the individual experiences of physicians who had used EXPAREL.

The guides, titled *Administration Technique Guide: Capturing Clinician Experience with EXPAREL*, were intended to summarize individual physicians' methodology for using EXPAREL in specific types of surgery. They set forth basic case information, patient characteristics, procedural details, follow-up notes, and administration technique. The guides also contained important safety information and other disclosures and disclaimers to allow physicians to make informed decisions on how best to treat their patients.

135. Pacira also stated, and discussed with physicians, that EXPAREL can provide pain relief for up to 72 hours. For instance, in a journal advertisement, Pacira referred to "Patient-Focused Pain Control That Lasts For Up To 72 Hours," and stated that EXPAREL is "[t]he only single-dose local analgesic to . . . [r]educe or eliminate opioids with pain control for up to 3 days." This claim was based on the successful primary endpoint of Pacira's pivotal trial in hemorrhoidectomies, which demonstrated, to a highly statistically significant degree, lower cumulative pain scores through 72 hours for EXPAREL patients compared to placebo patients.

136. Since the commercial launch of EXPAREL in 2012, Pacira has submitted numerous promotional materials to FDA using FDA Form 2253, as required by FDA regulations governing mandatory postmarketing reporting. 21 C.F.R. § 314.81(b)(3)(i). From the beginning, consistent with the EXPAREL label's broad indication, these promotional materials have touted the drug as approved for postsurgical administration into the surgical site to produce analgesia without limitation to hemorrhoidectomy and bunionectomy.

137. FDA has thus been on notice since April 2012 that Pacira was properly promoting EXPAREL as approved for surgeries other than hemorrhoidectomy and bunionectomy.

The Value of Pacira's Speech to Physicians and the Public Health

138. Surgeons, anesthesiologists, and other health care providers administer EXPAREL in various surgical sites consistent with the product's broad label. These physicians rely on information from Pacira in numerous ways.

139. In all surgical procedures, physicians rely on their experience administering local anesthetics. Physicians, including Plaintiffs, value information about EXPAREL's dosing and administration, and desire to receive such information from Pacira—including administration guides, which convey real-world experiences relating to physicians' use of EXPAREL in connection with a variety of different surgical procedures.

140. Physicians also value information about the existence of EXPAREL as an alternative to opioids. Prescribing physicians currently do not receive adequate information about alternatives to opioid drug treatment, which can lead to unnecessary prescriptions for opioids and thereby increase the risk of patients experiencing the adverse events associated with opioid use. The White House Office of National Drug Control Policy has explained that: "[m]ost [physicians and other prescribers and dispensers] receive little training on the importance of appropriate prescribing and dispensing of opioids to prevent adverse effects, diversion, and addiction." *See* Office of National Drug Control Policy, *Epidemic: Responding to America's Prescription Drug Abuse Crisis* 2 (2011), https://www.whitehouse.gov/sites/default/files/ondcp/policy-and-research/rx_abuse_plan.pdf.

141. Physicians value Pacira's speech regarding treatment options and alternatives to opioids because such information empowers them to make the best decisions for their patients, especially those most susceptible to the adverse events and risk for addiction associated with opioids.

The Government Bans Pacira's Speech and Threatens the Company

142. Three years after FDA approved EXPAREL with a broad indication "to produce postsurgical analgesia," it directed Pacira to cease promoting EXPAREL as a means "to produce postsurgical analgesia" in any surgical site apart from bunionectomies or hemorrhoidectomies.

143. FDA did not identify "new safety information" requiring revision of the approved label. 21 U.S.C. §§ 355(o)(4)(A), 355-1(a)(2)(A). And FDA did not make a formal determination or provide notice to Pacira, allowing Pacira to submit proposed labeling changes or challenge FDA's determination under the statutory frameworks applicable to post-approval changes to a drug's label. Those are the steps that would be necessary for FDA lawfully to change EXPAREL's approved label, but FDA took none of them. Indeed, FDA could not have amended EXPAREL's label consistent with the applicable law, because FDA could never meet the substantive requirements established under the FDCA for such a change.

144. Recognizing that it did not have a statutory or regulatory basis to narrow EXPAREL's label, FDA attempted to do so through its speech-restricting regulatory regime.

145. FDA sent Pacira a Warning Letter on September 22, 2014. The Warning Letter stated: "The approved labeling for Exparel does not provide instructions for, or otherwise indicate that Exparel will be safe and effective for postsurgical pain if used in surgical procedures other than hemorrhoidectomy or bunionectomy."

146. Citing administration guides used by Pacira to promote EXPAREL for use in particular surgical sites, consistent with EXPAREL's indication, the Warning Letter accused Pacira of promoting EXPAREL in a way that rendered it "misbranded within the meaning of the Federal Food, Drug, and Cosmetic Act . . . and make[s] it[s] distribution violative." Ignoring EXPAREL's track record of safety in procedures outside of bunionectomy and

hemorrhoidectomy, FDA asserted that "[t]hese violations are extremely concerning from a public health perspective because they provide evidence of the intended use of EXPAREL in surgical procedures other than those for which the drug has been shown to be safe and effective."

147. Contrary to FDA's own regulation stating that the Indications and Usage section controls the breadth of approved use, 21 C.F.R. § 201.57(c)(2)(iv), the Warning Letter focused only on the Dosage and Administration and Clinical Studies sections of the PI as the basis for arguing that EXPAREL was approved only for use in two specific surgical sites. FDA ignored the language in the Indications and Usage section of the PI, which states that EXPAREL is broadly "indicated for administration into the surgical site to produce postsurgical analgesia." Instead, the FDA Warning Letter accused Pacira of claiming that "EXPAREL is intended for new uses for which it lacks approval," and that these "violations . . . are serious."

148. FDA also asserted in the Warning Letter that it was "false or misleading" for Pacira to suggest that EXPAREL provides "pain control that lasts for up to 72 hours." But in fact, in its hemorrhoidectomy pivotal study, EXPAREL demonstrated highly statistically significant results on its primary endpoint, which assessed the area under the curve of the cumulative pain intensity scores for the first 72 hours following surgery. This endpoint, which FDA informed Pacira was appropriate to assess EXPAREL's efficacy before the pivotal study was initiated, reflects both magnitude *and* duration of effect. In addition, the Warning Letter ignored that the duration of effect of EXPAREL was further supported by multiple pre-specified secondary endpoints from the same trial. For example, the study showed with a high degree of statistical significance that 28% of patients receiving EXPAREL did not require rescue pain medication through 72 hours compared to only 10% of patients receiving placebo ($p<0.0001$). Ignoring the impressive results on the primary endpoint and pre-specified secondary endpoints,

the Warning Letter relied on a *post hoc* analysis to assert that EXPAREL is not effective for 72 hours. This analysis was based on inappropriate statistical methods; in particular, because the hemorrhoidectomy study was not statistically powerful enough to detect differences at various time points, FDA's conclusion that EXPAREL lost potency prior to 72 hours is not justifiable.

149. FDA demanded that "Pacira immediately cease violating the FD&C Act" and that Pacira formulate "a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audiences that received the violative promotional materials." The Warning Letter threatened that "[f]ailure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice."

150. Pacira strenuously disagreed with the allegations in the Warning Letter and attempted to engage OPDP on these issues. On October 6, 2014, Pacira submitted a comprehensive response to the Warning Letter, expressing strong disagreement with the suggestion that the challenged speech violated the FDCA, citing FDA's drug labeling regulations, the language in the EXPAREL PI, the approved indications of other pain drugs approved by FDA, and FDA's own draft guidance on the development of prescription pain medications. FDA refused to discuss the merits of Pacira's arguments, however, and Pacira was compelled to comply with FDA's demands.

151. In the face of the threats in the Warning Letter, Pacira agreed to take action to address each of FDA's demands. It issued "corrective" notices, which it developed in conjunction with and at the direction of FDA. In a February 4, 2015 letter to health care providers, Pacira noted that FDA issued a Warning Letter on September 22, 2014 requiring the corrective letter. Pacira maintained "that EXPAREL was approved for administration into the

surgical site to produce postsurgical analgesia," but added, as required by FDA, that "[a]pproval was based on studies of bunionectomy and hemorrhoidectomy, and the drug has not been demonstrated to be safe and effective for any other specific type of surgery."

152. Pacira was also required to state that FDA objected to claims that EXPAREL provides pain control that lasts for up to 72 hours, despite the fact that the primary endpoint of the FDA-approved pivotal trial substantiating that claim, in FDA's own words, "was chosen [because] it reflects both magnitude *and duration* of effect . . . in relieving pain," FDA Medical Review at 41 (emphasis added), and despite the fact that FDA's own medical reviewer acknowledged that EXPAREL "demonstrated a statistically significant reduction in pain through 72 hours compared to placebo ($p<0.0001$)," *id.* at 89.

153. Pacira was compelled to make these "corrective statements" in light of FDA's threat of enforcement action.

154. At the same time, Pacira continued to ask FDA to discuss these issues and sought to point out to FDA the gap between the Agency's exercise of its enforcement powers through the Warning Letter, and the applicable legal framework governing EXPAREL's label. In particular, Pacira, through its counsel, submitted a 32-page letter to FDA in June 2015 again requesting a meeting and explaining that EXPAREL's PI reflects FDA approval of the drug for a broad postsurgical analgesia indication not limited to bunionectomies and hemorrhoidectomies, that various analyses from the pivotal hemorrhoidectomy study support the claim that EXPAREL provides up to 72 hours of pain control, and that under the applicable regulatory framework, Pacira's speech about EXPAREL concerned on-label uses, and so was not forbidden under even FDA's cramped views of the law.

155. Pacira repeatedly sought to meet with FDA to discuss its position. But FDA refused to meet with Pacira. FDA acknowledged receipt of Pacira's June letter, but refused to respond to it. On July 24, 2015, FDA issued a "close-out" letter to Pacira referring again to Pacira's purportedly "violative" speech and its "corrective" action of discontinuing the challenged speech. That "close-out" letter omits Pacira's June letter from its recounting of the administrative record, appearing to erase the challenge Pacira had raised to FDA's contentions that Pacira's speech was "violative."

156. Pacira again wrote to FDA on August 25, 2015 to reiterate the views in its June letter and to again seek a meeting with FDA. As of September 8, 2015 FDA has not responded to that letter.

157. Based on FDA's position, Pacira fears enforcement action under the "new drug" and "misbranding" provisions of the FDCA.

158. The government's silencing of Pacira has already had tangible and harmful consequences for the Company. Pacira's sales are affected, its representatives are constrained in how they can speak with doctors and other health care professionals, and physicians now report being confused and uncertain about EXPAREL.

Pacira Desires to Resume Truthful and Non-Misleading Speech About EXPAREL

159. Pacira is a small company, which relies on a single product.

160. Pacira desires to speak in a truthful and non-misleading way about the use of EXPAREL in surgical sites other than bunionectomy and hemorrhoidectomy, consistent with the broad indication for which EXPAREL was approved. Physicians rely on information from Pacira to treat their patients. Without access to information from Pacira, physicians are hindered in their ability to care for patients.

161. Pacira desires to discuss with health care professionals that EXPAREL is a liposome injection of bupivacaine indicated for administration into the surgical site to produce postsurgical analgesia. More particularly, Pacira desires to discuss with health care professionals use of EXPAREL in specific surgical sites other than bunionectomy and hemorrhoidectomy. These include, but are not limited to: total knee arthroplasty; hip replacement; bariatric surgery; hernia repair; colectomy; cholecystectomy; ileostomy reversal; breast reconstruction; and urologic surgeries. Pacira also desires to discuss with health care professionals the different methods by which EXPAREL can be administered in surgical sites, including by infiltration of EXPAREL into the *transversus abdominis plane* ("TAP").

162. Pacira desires to discuss with health care professionals published studies and reports regarding EXPAREL's administration into different surgical sites.

163. Pacira further desires to discuss with health care professionals the experiences that other physicians have had administering EXPAREL into surgical sites to produce postsurgical analgesia.

164. Pacira also would like to discuss with health care professionals that EXPAREL has demonstrated effectiveness in some patients for up to 72 hours following surgery.

165. Pacira would also like to respond, in a truthful and non-misleading way, to speech by other companies comparing EXPAREL to other methods of treating postsurgical pain. In particular, Pacira would like to dispute Halyard's claims that ON-Q is superior to EXPAREL. Pacira would like to share with health care providers copies of scientific papers comparing EXPAREL with use of pain pups such as ON-Q in various settings, so that those providers can make informed decisions for their patients' postsurgical analgesic needs. Pacira would also like to provide information to health care providers about characteristics of pain pumps such as ON-

Q that are not associated with EXPAREL. For example, to use a device such as ON-Q, a catheter must be surgically inserted into the patient's body and connected to the pump. Catheters can migrate or dislodge, which may alter the location to which the pain medication in the pump is delivered. Patients may also be at risk of catheter-related infections.

166. Pacira would communicate the information described in paragraphs 160-165 above to health care professionals such as surgeons, anesthesiologists, and hospital and pharmacy administrators.

167. Pacira would communicate this information to health care professionals through proactive dissemination of written materials, publication of digital media, and engaging in oral discussions. The message in these forms of speech would be guided by and consistent with the information outlined in the paragraphs above. The information would be communicated in a manner that is truthful and non-misleading. Pacira would ensure that the speech is not misleading by providing appropriate disclosures or disclaimers.

168. Physicians would like to receive this information from Pacira. Physicians believe, based on their medical judgment, that access to this information and the ability to discuss these topics with Pacira would enable them to provide better care to their patients. Physicians also believe that Pacira is uniquely situated to provide this information, and that receiving this information would be of great value to patients experiencing postsurgical pain. And physicians believe that unless Pacira can proactively disseminate this information to them, they are unlikely to obtain the information at all.

LEGAL ARGUMENTS

Pacira Has a Right to Engage in Truthful and Non-Misleading Speech

169. Pacira's right to engage in truthful and non-misleading speech about the lawful uses of EXPAREL is well established. The government may only limit truthful, non-misleading speech about lawful activity when such restriction directly relates to a substantial state interest and is narrowly tailored to advance that interest. *Cent. Hudson*, 447 U.S. at 564; *Virginia State Bd. of Pharmacy v. Virginia Citizens Consumer Council*, 425 U.S. 748, 773 (1976).

170. Government action that singles out speech for restrictions based solely on the content of the message or the identity of the speaker requires a heightened scrutiny standard of review under the First Amendment. *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653, 2667 (2011). "Commercial speech is no exception," and the First Amendment's protection against "unjustified burdens on expression" has particular "relevance in the fields of medicine and public health, where information can save lives." *Id.* at 2664.

171. The Second Circuit has adjudicated this exact issue, and firmly rejected the premise of the FDA regulatory regime that truthful, non-misleading speech about lawful uses of FDA-approved drugs can be criminalized. In *Caronia*, the court held that "the government cannot prosecute pharmaceutical manufacturers and their representatives under the FDCA for speech promoting the lawful, off-label use of an FDA-approved drug." 703 F.3d at 169. Since the FDCA and FDA regulations "reference 'promotion' only as evidence of a drug's intended use," the court employed the canon of constitutional avoidance to "construe the FDCA as not criminalizing the simple promotion of a drug's off-label use because such a construction would raise First Amendment concerns." *Id.* at 160.

172. And as Judge Engelmayer recently confirmed, the Second Circuit's holding is "categorical," establishing that it is not "constitutionally permissible" to prohibit truthful and non-misleading speech from a pharmaceutical manufacturer when that speech alone is the "proscribed conduct." *Amarin*, slip op. at 47. That is, "truthful and non-misleading speech promoting the off-label use of an FDA-approved drug . . . *cannot* be the act upon which an action for misbranding is based." *Id.* at 49.

173. The arguments advanced by the government in *Amarin* for prohibiting manufacturer speech, each rejected by the court in that case, are even less persuasive here. FDA's primary argument for prohibiting off-label speech was that allowing "truthful speech aimed at promoting off-label drug use is a 'frontal assault . . . on the framework for new drug approval that Congress created in 1962.'" *Id.* at 49 (quoting Gov't oral argument). As Judge Engelmayer concluded in dismissing this argument, however, these statutory provisions predate modern First Amendment doctrine, and so must be considered in light of the constitutional protections afforded under contemporary precedent. *Id.* The government's argument would be even more misplaced with respect to Pacira's speech at issue here, since Pacira observed rather than evaded the FDCA's drug approval regime when it obtained a broad indication for use of EXPAREL in surgical sites generally.

174. FDA's closely related second and third arguments in *Amarin* were that the government could prohibit statements that are "more likely to reflect a manufacturer's intent to promote off-label use," *id.* at 50, and that the government could rely on truthful and non-misleading statements "to establish, in a misbranding action, that the defendant intended to promote off-label use," *id.* at 51. Each of these arguments advanced by the government based on the speaker's *intent* was rejected by Judge Engelmayer, because *Caronia* turned on the *actus*

reus requirement—it held that "the act of truthful and non-misleading speech promoting off-label use," *id.* at 50, could not be criminalized. Of course, in this case, Pacira contends that its desired speech is *within* the indication already approved by FDA. But even if use of EXPAREL in specific surgical sites beyond bunionectomy and hemorrhoidectomy were "off-label," such use would be lawful, and Pacira's truthful and non-misleading speech about such use could not be deemed "violative" of the FDCA, as FDA has threatened.

Pacira's Speech Is Truthful, Non-Misleading, and Consistent with EXPAREL's Approved Indication

175. Pacira's speech regarding the use of EXPAREL for postsurgical pain management for procedures other than bunionectomies and hemorrhoidectomies is truthful and non-misleading.

176. Pacira reasonably and in good faith believes that its speech concerns on-label uses of EXPAREL. FDA has recognized the difficulty in studying and quantifying pain, and has issued guidance clarifying that clinical trials evaluating drugs in two different clinical models are all that is required for FDA to approve a broad pain indication. Pacira's actions were consistent with these requirements, and Pacira received a broad postsurgical indication as a result. Pacira's subsequent promotion of EXPAREL, consistent with this general indication, is therefore truthful, non-misleading, "on-label" speech.

177. FDA's decision to require Pacira to conduct pediatric studies of EXPAREL under PREA makes clear that the approved indication for EXPAREL cannot be limited to bunionectomies and hemorrhoidectomies.

178. FDA's guidance documents and prior precedent further support Pacira's view that EXPAREL was granted a broad "postsurgical" indication that was not limited to the specific surgical procedures of bunionectomies and hemorrhoidectomies. FDA's historical practice

relating to other drugs also makes clear that for analgesics, approving a broad indication based on clinical studies in a limited subpopulation is ordinary practice. FDA's guidance stating that clinical trials evaluating drugs in two different clinical models are all that is required for FDA to approve a broad pain indication further demonstrate FDA's preference for extrapolating to broad pain indications on the basis of studies in limited clinical settings. Thus, because the mechanism of action of bupivacaine, the active ingredient in EXPAREL, is well known, and because the clinical studies of EXPAREL in bunionectomy and hemorrhoidectomy encompassed opposite ends of the spectrum of the human anatomy, FDA appropriately extrapolated from those studies and granted EXPAREL a broad postsurgical indication, as evidenced by the Indications and Usage section of the label.

179. FDA's regulations make clear that the Indications and Usage section of the label defines the approved indication for a product. 21 C.F.R. § 201.57(c)(2)(iv).

180. The Indications and Usage section of the approved label for EXPAREL states that EXPAREL is "indicated for administration into the surgical site to produce postsurgical analgesia."

181. Pacira reasonably and in good faith views its speech to be "on-label" and so permissible even under the government's own restrictive view of the legal framework. Pacira complied with current FDA guidance regarding the necessary steps to achieve a broad pain indication and received FDA approval for a label with a broadly worded Indications and Usage section that rejected internal FDA efforts to narrow the approved uses.

182. Pacira's speech is not misbranding, or "false and misleading," 21 U.S.C. § 352(a), because it is consistent with the broad indication Pacira received for EXPAREL and with the scientific basis behind that approved indication.

183. But even if Pacira's approval and indication were limited to use in the surgical site for patients undergoing bunionectomy and hemorrhoidectomy—which, by its express terms, it is not—its proposed speech about use in other surgical sites would still be truthful, non-misleading, and constitutionally protected. In light of scientific and medical consensus about the ability to draw general conclusions about the safety and effectiveness of pain medications based on two trials, Pacira's promotion of EXPAREL for use in other surgical sites would be truthful and non-misleading. As such, it could not be prohibited or criminalized, even if it constituted an off-label use.

184. Pacira's indisputably "on-label" proposed speech, including about EXPAREL's effectiveness for 72 hours and its rebuttal of competitors' criticisms, are also truthful and non-misleading, and so constitutionally protected. FDA's regulations preclude Pacira from making any statements about the effectiveness of EXPAREL, or comparing it to other products, unless those statements are supported by "substantial evidence," which FDA generally construes as two randomized, blinded, and well-controlled clinical trials with pre-specified endpoints. 21 C.F.R. §§ 202.1(e)(6)(i), (ii); 314.126(a). Proactively distributing scientific papers comparing ON-Q with EXPAREL or sharing information about potentially undesirable issues associated with pain pumps such as ON-Q would be treated by FDA as an implied superiority claim subject to this exceptionally high "substantial evidence" standard. FDA's categorical criminalization of manufacturer speech not supported by multiple well-controlled, randomized clinical studies cannot be squared with the First Amendment's protection of truthful and non-misleading speech and prohibition on content- and speaker-based restrictions.

185. In addition, FDA cannot categorically prohibit speech on the theory that it is "inherently" false or misleading when adequate disclosures or disclaimers could render the

speech not misleading. "[W]hen government chooses a policy of suppression over disclosure—at least where there is no showing that disclosure would not suffice to cure misleadingness—government disregards a 'far less restrictive' means." *Pearson v. Shalala*, 164 F.3d 650, 658 (D.C. Cir. 1999); *see Amarin*, slip op. at 57-61 (describing how proposed disclosures render off-label claims non-misleading). Yet FDA's regulations are categorical in nature, and FDA did not consider that such claims could be made with further qualification.

Pacira's Speech Serves an Important Public Health Interest, Including by Providing Information to Physicians About Alternatives to Opioids

186. Pacira's exercise of its speech rights generates significant benefits for physicians, their patients, and the public at large.

187. Sophisticated health care providers and others have a constitutionally protected interest in the free flow of information that could enable better educated decisions about patient care and thus improve public health. *See Sorrell*, 131 S. Ct. at 2671-72; *see also Va. State Bd. of Pharm.*, 425 U.S. at 757 n.15 (recognizing the "independent [First Amendment] right of the listener to receive information sought to be communicated").

188. As explained earlier, the use of opioids for certain patients is associated with the occurrence of a range of adverse events, and over time has been shown to be correlated with an increased risk of addiction. In addition, the government itself has acknowledged that prescribing physicians lack adequate training with respect to responsible opioid prescribing, which has exacerbated the nationwide opioid abuse epidemic. Pacira's speech about the value of EXPAREL as an alternative to prescription opioids thus serves an important public health interest by equipping providers with improved knowledge about the range of options available for treating the most vulnerable patients.

The Government Has Violated Pacira's and the Listeners' First Amendment Rights

189. FDA's interpretation of the relevant FDCA provisions, as applied to Pacira, prohibits truthful and non-misleading speech about EXPAREL. Such a result violates the First Amendment rights of Pacira and its listeners, and is plainly inconsistent with controlling Supreme Court and Second Circuit precedent.

190. Because Pacira's speech is truthful and non-misleading and does not concern unlawful activity, it is protected under the First Amendment. *See Cent. Hudson*, 447 U.S. at 564. This protection applies regardless of whether Pacira's speech is classified as "on label" or "off label." *Caronia*, 703 F.3d at 163-65; *Sorrell*, 131 S. Ct. at 2662-64.

191. As laid out in its Warning Letter, FDA has forbidden Pacira from engaging in speech related to lawful uses of EXPAREL that are not specifically listed on the EXPAREL label. Such restrictions, combined with the government's related threats of enforcement action, have prompted Pacira to cease certain communications about EXPAREL relating to uses FDA has retroactively declared "off-label" and to refrain from engaging in the proposed speech. The government's actions thus have created an impermissible chilling effect on Pacira's protected truthful and non-misleading speech in violation of the First Amendment.

192. Pacira faces a real and imminent threat that the government will take enforcement action against it to prevent or punish its proposed speech. As outlined above, FDA's Warning Letter sets out in no uncertain terms FDA's view that Pacira's communications regarding the use of EXPAREL in surgeries other than hemorrhoidectomy and bunionectomy violate the FDCA. The Warning Letter directly threatens that the government will initiate enforcement action "without further notice," unless Pacira ceases such communications.

193. The government has aggressively prosecuted pharmaceutical manufacturers for alleged "off-label" promotion based on its interpretations of the FDCA's "new drug" and "misbranding" provisions. *See, e.g.*, Press Release, DOJ, Endo Pharmaceuticals and Endo Health Solutions to Pay $192.7 Million to Resolve Criminal and Civil Liability Relating to Marketing of Prescription Drug Lidoderm for Unapproved Uses (Feb. 21, 2014) ("Endo Release"), http://www.justice.gov/opa/pr/endo-pharmaceuticals-and-endo-health-solutions-pay-1927-million-resolve-criminal-and-civil; Press Release, DOJ, Johnson and Johnson to Pay More Than $2.2 Billion to Resolve Criminal and Civil Investigations (Nov. 4, 2013) ("J&J Release"), http://www.justice.gov/opa/pr/johnson-johnson-pay-more-22-billion-resolve-criminal-and-civil-investigations; Press Release, DOJ, Wyeth Pharmaceuticals Agrees to Pay $490.9 Million for Marketing the Prescription Drug Rapamune for Unapproved Uses (July 30, 2013), http://www.justice.gov/opa/pr/wyeth-pharmaceuticals-agrees-pay-4909-million-marketing-prescription-drug-rapamune-unapproved. Such prosecutions have targeted truthful and non-misleading speech in addition to speech that is false and/or misleading.

194. In addition, the government has threatened to undertake such enforcement actions in the future. For example, in February 2014, Mark Dragonetti, Special Agent in Charge of FDA's Office of Criminal Investigations' New York Field Office, stated that FDA will continue to pursue enforcement actions against pharmaceutical companies for sharing "off-label" information. Endo Release.

The Government's Approach Is Arbitrary and Capricious and Fails to Provide Fair Notice of What Speech It Considers Criminal

195. FDA's restrictions of Pacira's speech also violate the Company's rights under the Fifth Amendment and the Administrative Procedures Act (APA).

196. FDA has changed its position about EXPAREL's approved Indication in a manner contrary to law and science, and without following the proper procedures set forth in the law and regulations. In its October 28, 2011 approval of Pacira's NDA application, FDA approved EXPAREL "for administration into the surgical site to produce postsurgical analgesia." FDA did not approve EXPAREL for this broad indication without considering the breadth of the language, and it was not accidental that EXPAREL received an indication that extended beyond bunionectomy and hemorrhoidectomy. To the contrary, FDA specifically rejected the suggestion of FDA Medial Officer Dr. Arthur Simone to limit EXPAREL's indication to "postoperative analgesia following hemorrhoidectomy and bunionectomy." FDA's approval of EXPAREL for administration into any surgical site is further evidenced by the pediatric studies of EXPAREL that FDA is requiring Pacira to conduct. Because FDA only has authority to require on-label pediatric studies, and because bunionectomies and hemorrhoidectomies rarely occur in the pediatric population, FDA could only have reached a conclusion that pediatric studies were required for EXPAREL if it understood the product's approved indication to encompass all surgical sites generally, and not just those sites associated with bunionectomies and hemorrhoidectomies. And if FDA understood EXPAREL's approved indication to be limited to surgical sites associated with bunionectomies and hemorrhoidectomies, it would have been unethical for FDA to have required evaluation of EXPAREL in children in other, unapproved surgical sites.

197. In the September 22, 2014 Warning Letter, however, FDA reversed course, accusing Pacira of "misbranding" EXPAREL by promoting it for uses other than hemorrhoidectomy and bunionectomy. FDA made this abrupt change despite approving EXPAREL for a broad indication and despite having remained silent for several years following

Pacira's submission to FDA for its review of promotional materials aimed at medical professionals stating that EXPAREL has been demonstrated to be safe and effective in various other surgical procedures, including knee arthroplasty, open hysterectomy, and adominoplasty, among others.

198. In addition to failing to explain or justify its reversal, FDA failed to meet or follow necessary requirements and procedures as set out in its own regulations. FDA may not unilaterally revise a product's approved label or force a manufacturer to accept a revision through enforcement mechanisms, as FDA is attempting to do with EXPAREL. FDA may only pursue such a change in limited circumstances, such as through identifying new safety information, which do not exist for EXPAREL.

199. Even if FDA could now change the labeled indication for EXPAREL, it could not do so retroactively. Nor may it accomplish the same impermissible retroactive effect by reinterpreting EXPAREL's label to be narrower than the language provides. Especially where First Amendment interests are at stake, the government must provide clear warning of when speech would constitute a criminal violation. Even if EXPAREL's label were susceptible of a narrow reading limited to bunionectomy and hemorrhoidectomy, it was not clearly so circumscribed, and Pacira had insufficient warning of what speech might be deemed criminal. Pacira followed the correct approval process, conducted appropriate clinical trials, received a broad indication, spoke about EXPAREL consistent with that regulation, and years after the fact has been accused of misconduct that is subject to regulatory and criminal penalties.

CLAIMS FOR RELIEF

COUNT I: THE FIRST AMENDMENT

FDA's interpretation of the FDCA and its regulations violates the First Amendment by restricting Pacira's ability to engage in protected, truthful and non-misleading speech about EXPAREL.

200. Pacira realleges and incorporates by reference the preceding allegations in paragraphs 1 through 199 as though fully set out herein.

201. The First Amendment protects Pacira's truthful, non-misleading speech regarding and the efficacy of EXPAREL for postsurgical administration of EXPAREL in surgical sites other than bunionectomy and hemorrhoidectomy, its ability to control pain for up to 72 hours, and its comparative benefits versus other drugs and devices.

202. By broadly defining "labeling" to encompass all tangible materials distributed by the manufacturer that contain manufacturer-supplied drug information, 21 C.F.R. § 202.1(l)(2), FDA has asserted authority over virtually all speech by a manufacturer about its product, in a manner inconsistent with the First Amendment and unsupported by the FDCA.

203. FDA deems any drug "misbranded" if its "labeling" lacks "adequate directions for use." *See* 21 U.S.C. § 352(f)(1). Although Congress did not intend this provision to apply to prescription drugs, FDA has adopted regulations requiring that labeling for any prescription drug contain "adequate information" for any "use for which [the drug] is intended," including "all purposes for which [the drug] is advertised or represented." 21 C.F.R. § 201.100(c)(1). At the same time, FDA forbids that "labeling" from speaking about any use other than the use described in the labeling approved by FDA. *Id.* § 202.1(e)(4)(i)(a). In this way also, FDA criminalizes truthful and non-misleading manufacturer speech about lawful uses of the company's product unless and until approved by FDA.

204. FDA's Warning Letter invokes these prohibitions to stop Pacira from discussing the effective medical use of EXPAREL in surgical sites outside of hemorrhoidectomy and bunionectomy, even though FDA has approved EXPAREL's use "for administration into the surgical site to produce postsurgical analgesia," without limitation as to any particular surgical site. Promoting EXPAREL for use in surgical sites other than hemorrhoidectomy and bunionectomy is supported by sound science, which permits extrapolating about general application of an analgesic from studies of that analgesic's safety and efficacy in different locations, such as the successful pivotal studies of EXPAREL's use in soft and hard tissues. The truthful nature of such statements is supported by FDA's own reliance on such extrapolation in adopting the broad indication language for EXPAREL and other pain medications. FDA's prohibition against Pacira providing surgeons and anesthesiologists further information about the use of EXPAREL in these other surgical sites violates the First Amendment.

205. The FDCA prohibits a manufacturer from introducing a drug into interstate commerce if its "labeling" is "false or misleading in any particular." 21 U.S.C. §§ 331(a), 352(a). FDA has interpreted the phrase "false or misleading in any particular" to preclude Pacira from making any statements about the effectiveness of EXPAREL, *see* 21 C.F.R. § 202.1(e)(1), or comparing it to other products, unless those statements are supported by "substantial evidence," which FDA construes as two adequate and well-controlled randomized clinical trials. 21 U.S.C. § 355(d)(7); 21 C.F.R. § 202.1(e)(6)(i)-(ii). FDA's categorical criminalization of all speech not supported by well-controlled, randomized clinical studies with pre-specified endpoints cannot be squared with the First Amendment, which recognizes that speech cannot be categorically prohibited as "false or misleading" when adequate disclosures would render the speech truthful. As applied to Pacira's desired speech regarding EXPAREL's effectiveness to

control pain for up to 72 hours and its effectiveness in comparison to the ON-Q pump, FDA's categorical test for whether speech is "misleading" violates the First Amendment of the Constitution.

206. The FDCA prohibits introducing "misbranded" drugs from entering into interstate commerce, and deems a drug "misbranded" if its advertising fails to include a "true statement" regarding the drug, including a "brief summary relating to side effects, contraindications, and effectiveness." 21 U.S.C. § 352(n)(3). FDA has expanded this provision to forbid any manufacturer from "recommend[ing] or suggest[ing] any use that is not in the labeling accepted in [the drug's] approved new-drug application." 21 C.F.R. § 202.1(e)(4)(i)(a). FDA therefore explicitly forbids Pacira from distributing truthful and non-misleading direct-to-physician advertisements suggesting an off-label use of EXPAREL, despite the fact that such use is lawful.

207. Pacira has no adequate remedy at law.

208. Pacira therefore seeks entry of a judgment declaring that FDA's application of 21 U.S.C. §§ 331(a), (d), 352(f), (n), 355(a), and 21 C.F.R. §§ 201.5, 201.100, 201.115, 201.128, 202.1(e)(4)(i)(a), 202.1(e)(6)(i) and (ii), 202.1(l)(2), violate the First Amendment as interpreted by FDA and as applied to prohibit Pacira categorically from engaging in promotional speech with sophisticated audiences about the use of EXPAREL in surgical sites other than bunionectomy and hemorrhoidectomy, the ability of EXPAREL to control pain for up to 72 hours, and comparisons of EXPAREL's effectiveness to other products (even if not supported by "substantial evidence" as defined by FDA).

COUNT II: THE ADMINISTRATIVE PROCEDURE ACT (APA)

FDA's unilateral attempt to modify Pacira's approved indication by asserting in the Warning Letter that Pacira's speech is off-label is arbitrary, capricious, in excess of the Agency's statutory authority, and fails to observe the procedure required by law for modifying a drug's label.

209. Pacira realleges and incorporates by reference the preceding allegations in paragraphs 1 through 208 as though fully set out herein.

210. FDA's assertion in its Warning Letter that Pacira's speech about the use of EXPAREL in "surgical sites to produce postsurgical analgesia" is off-label is arbitrary, capricious and not in accordance with the FDCA and FDA's own regulations.

211. Under the FDCA, applicants must seek labeling approval for a "new drug" or risk criminal penalties. 21 U.S.C. §§ 331, 333. All "new drug" applicants therefore must comply with FDA's labeling approval regime, which requires applicants to submit a comprehensive application supported by well-designed clinical trials. *Id.* § 355. The outcome of this thorough process is the FDA-approved label, which includes the Indications and Usage section that states the indications for which the drug has been approved. 21 C.F.R. § 201.57(a)(6), (c)(2).

212. Other sections of the FDA-approved label provide additional important information about the safe and effective use of the drug. But these do not limit the breadth of the "indication" for which the drug is approved, which must be stated in the "Indications and Usage" section of the label. 21 C.F.R. § 201.57(a)(6), (c)(2).

213. EXPAREL's FDA-approved label states in the "Indications and Usage" that "EXPAREL is a liposome injection of bupivacaine, an amide-type local anesthetic, indicated for administration into the surgical site to produce postsurgical analgesia." Besides indicating that EXPAREL is not indicated for use in patients under 18 years of age, the "Indications and Usage"

section of EXPAREL's label does not limit the surgical sites for which it is approved to produce postsurgical analgesia.

214. FDA's assertion in its Warning Letter that Pacira's promotion of EXPAREL for use to produce postsurgical analgesia in surgical sites other than bunionectomy and hemorrhoidectomy constituted "new uses for which [EXPAREL] lacks approval" is arbitrary and capricious and contrary to the FDCA and FDA's own guidance and regulations. FDA is attempting to change EXPAREL's approved indications without identifying "new safety information" such as "information derived from a clinical trial, an adverse event report, a postapproval study [or other data regarding] a serious risk associated with use of the drug that the Secretary has become aware of . . . since the drug was approved," as would be required to adopt a formal change to EXPAREL's label. 21 U.S.C. §§ 355-1(b)(3), 355(o)(2)(C). FDA similarly failed to find that EXPAREL's labeling was "false or misleading in any particular," which is unsurprising given FDA's earlier approval. *Id.* § 355(e); 21 C.F.R. § 314.150(b)(3).

215. When FDA seeks to modify an approved label, it must allow an NDA holder time to submit proposed labeling changes or challenge FDA's determination. *See*, *e.g.*, 21 U.S.C. § 355(o)(4)(F). FDA may not deploy its enforcement tools, including Warning Letters, to unilaterally revise, amend, or order revisions to an approved label.

216. FDA refuses to honor the broad indication it approved for EXPAREL following the enumerated approval process. FDA also seeks to revoke EXPAREL's broad indication without following the statutory and regulatory provisions granting FDA limited authority to modify an approved label only in certain circumstances. FDA's actions are "not in accordance with law" and are "in excess of statutory jurisdiction, authority, or limitations, or short of statutory right." 5 U.S.C. § 706(2)(A), (C).

217. Pacira has no adequate remedy at law.

218. Pacira therefore seeks entry of a judgment declaring that FDA's attempt to modify Pacira's approved Indication through a Warning Letter, or to apply any of the provisions listed in ¶ 208 to this effect, is arbitrary, capricious, in excess of the Agency's statutory authority, and fails to meet the standards and observe the procedures required by law for modifying a drug approval.

COUNT III: THE FIFTH AMENDMENT

FDA's regulations as applied to Pacira are vague, deprive the company of fair notice of what is prohibited, and operate as a retroactive, ex post facto penalty, all in violation of the Due Process Clause of the Fifth Amendment.

219. Pacira realleges and incorporates by reference the preceding allegations in paragraphs 1 through 218 as though fully set out herein.

220. Under FDA's interpretation of its regulations and the FDCA, a drug is criminally misbranded if it is "advertised or represented" for any use not approved by FDA. *See* 21 U.S.C. §§ 331(a), 333(a); 21 C.F.R. §§ 201.100(c)(1), 202.1(e)(4)(i)(a). As-applied, FDA's regulations prohibit any promotion—regardless of how truthful and non-misleading the promotion would be—of EXPAREL for any off-label use. The Second Circuit has ruled that the FDCA cannot "criminaliz[e] the simple promotion of a drug's off-label use" because of First Amendment concerns. Yet FDA has failed to clarify what off-label promotion, if any, is permitted after *Caronia*.

221. The Due Process Clause of the Fifth Amendment requires agencies to establish clear rules that give "fair notice of what is prohibited." *FCC v. Fox Television Studios*, 132 S. Ct. 2307, 2317 (2012). "When speech is involved, rigorous adherence to [these] requirements is necessary to ensure that ambiguity does not chill protected speech." *Id.* at 2317. FDA has failed

to provide these requirements, instead creating uncertainty and doubt about what FDA views as permissible versus impermissible speech, violating Pacira's right to due process under the Due Process Clause of the Fifth Amendment.

222. This violation is particularly egregious in Pacira's case. FDA granted Pacira a broad indication for controlling postsurgical pain in any "surgical site" and allowed Pacira to promote consistent with that indication for years. Three years later, FDA appears to have concluded that Pacira should have received a narrower indication, and accused Pacira of criminal activity for supposedly *off-label* speech. As applied to Pacira's promotion of EXPAREL for surgical sites other than bunionectomy or hemorrhoidectomy, FDA's prohibition on off-label promotion would constitute a retroactive, ex post facto penalty in violation of the Due Process Clause.

223. Pacira has no adequate remedy at law.

224. Pacira therefore seeks entry of a judgment declaring that FDA's regulations, as set forth in ¶ 208, as applied to Pacira are unconstitutional or invalid because they are vague, deprive the company of fair notice of what is prohibited, and operate as a retroactive, ex post facto penalty, all in violation of the Due Process Clause.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request that this Court enter judgment in its favor and that the Court:

(A) Declare that FDA may not, under the FDCA and consistent with the First Amendment, limit Pacira's communications to health care providers regarding FDA-approved uses of EXPAREL, which include use in surgical sites without limitation.

(B) Declare that 21 C.F.R. § 202.1(*l*)(2) is invalid under the FDCA and the First Amendment insofar as it would restrict Pacira's truthful and non-misleading speech.

(C) Declare that 21 U.S.C. § 352(a) does not encompass, or is unconstitutional as applied to, Pacira's truthful and non-misleading speech.

(D) Declare that 21 C.F.R. §§ 202.1(e)(4)(i)(a) and 202.1(e)(6) are invalid under the FDCA and the First Amendment insofar as they restrict Pacira's truthful and non-misleading speech.

(E) Declare that 21 C.F.R. §§ 201.5 and 201.100 are invalid under the FDCA and the First Amendment insofar as they restrict Pacira's truthful and non-misleading speech.

(F) Declare that FDA's attempt to modify Pacira's approved Indication through a Warning Letter is arbitrary, capricious, in excess of the Agency's statutory authority, and fails to observe the procedure required by law for modifying a drug approval.

(G) Declare that FDA's regulations as applied to Pacira are unconstitutional or invalid because they are vague, deprive the company of fair notice of what is prohibited, and operate as a retroactive, ex post facto penalty, all in violation of the Due Process Clause.

(H) Enter a preliminary injunction enjoining FDA and the individual defendants from taking any action during the pendency of this litigation to enforce the aforementioned provisions against Pacira based on Pacira's proposed truthful and non-misleading speech regarding its medications, and thereby protect Pacira's First Amendment rights from ongoing harm while this litigation is pending;

(I) Enter a permanent injunction enjoining FDA and the individual defendants from taking any action to infringe upon Pacira's protected First Amendment right to engage in truthful and non-misleading speech;

(J) Award attorney's fees and costs as the court deems equitable and just;

(K) Award such other and further relief that the court deems equitable and just.

This 8th day of September, 2015.

Respectfully submitted,

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